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Box PATENT APPLICATION
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Sir:

Transmitted herewith for filing is a continuation of U.S. Application Serial No. 09/069,226, filed April 27, 1998, now pending, and issuing on January 11, 2000 as U.S. Patent No. 6,013,509, herein incorporated by reference, for:

Inventor(s): PATRICK V. WARREN and RONALD V. SWANSON

For: **TRANSAMINASES AND AMINOTRANSFERASES**

Enclosed are the following papers, including all those required for a filing date under 37 CFR § 1.53(b):

	# of Pages
Specification	59
Claims	3
Abstract	1
Formal Drawings [# of Sheets]	18
Combined Declaration and Power of Attorney	[To be filed at a later date]
Small Entity Declaration	1
Permission to Use Sequence Listing and Paper Copy	35
Information Disclosure Statements	2
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Filing fee to be charged to Deposit Account No. 07-1895 in amount of zero

This application claims priority under 35 U.S.C. § 120 to U.S. Patent Application No. 09/069,226, filed April 27, 1998 and issued on January 11, 2000 as U.S. Patent No. 6,013,509; which is a continuation of U.S. Patent Application No. 08/599,171, filed February 9, 1996 and issued on September 29, 1999 as U.S. Patent No. 5,814,473, the contents of all of which are all incorporated by reference in their entirety herein.

No payment of the issue fee, abandonment of, or termination of proceeding has occurred in the above-identified prior application.

The payment of the filing fee is to be deferred until the executed Declaration is filed. Do not charge our deposit account.

Amend the specification by inserting after the title on page 1:

This application is a continuation of U.S. Patent Application No. 09/069,226, filed April 27, 1998 and issued on January 11, 2000 as U.S. Patent No. 6,013,509; which is a continuation of U.S. Patent Application No. 08/599,171, filed February 9, 1996 and issued on September 29, 1999 as U.S. Patent No. 5,814,473, the entire contents of which are hereby incorporated herein by reference.

A verified statement claiming small entity status was filed in parent application, Serial No. 09/069,226, filed on April 27, 1998, and such status is still proper.

The prior application is assigned of record to Recombinant Biocalaysis, Inc., on Reel 8051, Frame 0113 on April 26, 1996.

The power of attorney in the prior application is to Lisa A. Haile, Registration No. 38,347.

A copy of the prior application as filed is enclosed, including a copy of a Combined Declaration and Power of Attorney filed in parent application, U.S. Application Serial No. 09/069,226, filed on April 27, 1998.

Permission to Use Sequence Listing of parent priority is enclosed along with paper copy of Sequence Listing.

Information Disclosure Statements filed in the prior application under 37 C.F.R. 1.97 are hereby made of record. Copy of PTO-1449 form is enclosed.

Address all future communications to:

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The undersigned states that the enclosed application papers comprise a copy of the prior application as filed.

Respectfully submitted,

Date: January 11, 2000

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APPLICATION

in the name of

Patrick V. Warren and Ronald V. Swanson

of

Diversa

for

TRANSAMINASES AND AMINOTRANSFERASES

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TRANSAMINASES AND AMINOTRANSFERASES

This application is a Continuation of U.S. Patent Application No. 08/599,171 filed on February 9, 1996.

This invention relates to newly identified polynucleotides, polypeptides encoded by such polynucleotides, the use of such polynucleotides and polypeptides, as well as the production and isolation of such polynucleotides and polypeptides. More particularly, the polynucleotides and polypeptides of the present invention have been putatively identified as transaminases and/or aminotransferases. Aminotransferases are enzymes that catalyze the transfer of amino groups from α-amino to α-keto acids. They are also called transaminases.

The α-amino groups of the 20 L-amino acids commonly found in proteins are removed during the oxidative degradation of the amino acids. The removal of the α-amino groups, the first step in the catabolism of most of the L-amino acids, is promoted by aminotransferases (or transaminases). In these transamination reactions, the α-amino group is transferred to the α-carbon atom of α-ketoglutarate, leaving behind the corresponding α-keto acid analog of the amino acid. There is no net deamination (*i.e.*, loss of amino groups) in such reactions because the α-ketoglutarate becomes aminated as the α-amino acid is deaminated. The effect of transamination reactions is to collect the amino groups from many different amino acids in the form of only one, namely, L-glutamate. The glutamate channels amino groups either into biosynthetic pathways or into a final sequence of reactions by which nitrogenous waste products are formed and then excreted.

Cells contain several different aminotransferases, many specific for α-ketoglutarate as the amino group acceptor. The aminotransferases differ in their specificity for the other substrate, the L-amino acid that donates the amino group, and

are named for the amino group donor. The reactions catalyzed by the aminotransferases are freely reversible, having an equilibrium constant of about 1.0 ($\Delta G^{0'} \simeq 0$ kJ/mol).

Aminotransferases are classic examples of enzymes catalyzing bimolecular ping-pong reactions. In such reactions the first substrate must leave the active site before the second substrate can bind. Thus the incoming amino acid binds to the active site, donates its amino group to pyridoxal phosphate, and departs in the form of an α-keto acid. Then the incoming α-keto acid is bound, accepts the amino group from pyridoxamine phosphate, and departs in the form of an amino acid.

The measurement of alanine aminotransferase and aspartate aminotransferase levels in blood serum is an important diagnostic procedure in medicine, used as an indicator of heart damage and to monitor recovery from the damage.

The polynucleotides and polypeptides of the present invention have been identified as transaminases and/or aminotransferases as a result of their enzymatic activity.

In accordance with one aspect of the present invention, there are provided novel enzymes, as well as active fragments, analogs and derivatives thereof.

In accordance with another aspect of the present invention, there are provided isolated nucleic acid molecules encoding the enzymes of the present invention including mRNAs, cDNAs, genomic DNAs as well as active analogs and fragments of such enzymes.

In accordance with another aspect of the present invention there are provided isolated nucleic acid molecules encoding mature polypeptides expressed by the DNA contained in ATCC Deposit No. _____.

In accordance with yet a further aspect of the present invention, there is provided a process for producing such polypeptides by recombinant techniques comprising culturing recombinant prokaryotic and/or eukaryotic host cells, containing a nucleic acid sequence of the present invention, under conditions promoting expression of said enzymes and subsequent recovery of said enzymes.

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing such enzymes, or polynucleotides encoding such enzymes for transferring an amino group from an α-amino acid to an α-keto acid. Most transaminases use L-amino acids as substrates, but as described below, it is also possible to convert the transaminases of the invention to use D-amino acids as substrates, thereby increasing their array of uses to include, for example, manufacture of synthetic pyrethroids and as components of β-lactam antibiotics. The transaminases of the invention are stable at high temperatures and in organic solvents and, thus, are superior for use with L- and/or D-amino acids for production of optically pure chiral compounds used in pharmaceutical, agricultural and other chemical industries.

In accordance with yet a further aspect of the present invention, there are also provided nucleic acid probes comprising nucleic acid molecules of sufficient length to hybridize to a nucleic acid sequence of the present invention.

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing such enzymes, or polynucleotides encoding such enzymes, for *in vitro* purposes related to scientific research, for example, to generate probes for identifying similar sequences which might encode similar enzymes from other organisms by using certain regions, *i.e.*, conserved sequence regions, of the nucleotide sequence.

These and other aspects of the present invention should be apparent to those skilled in the art from the teachings herein.

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

Figure 1 is an illustration of the full-length DNA (SEQ ID NO:17) and corresponding deduced amino acid sequence (SEQ ID NO:25) of *Aquifex* aspartate transaminase A of the present invention. Sequencing was performed using a 378 automated DNA sequencer (Applied Biosystems, Inc.) for all sequences of the present invention.

Figure 2 is an illustration of the full-length DNA (SEQ ID NO:18) and corresponding deduced amino acid sequence (SEQ ID NO:26) of *Aquifex* aspartate aminotransferase B.

Figure 3 is an illustration of the full-length DNA (SEQ ID NO:19) and corresponding deduced amino acid sequence (SEQ ID NO:27) of *Aquifex* adenosyl-8-amino-7-oxononanoate aminotransferase.

Figure 4 is an illustration of the full-length DNA (SEQ ID NO:20) and corresponding deduced amino acid sequence (SEQ ID NO:28) of *Aquifex* acetylornithine aminotransferase.

Figure 5 is an illustration of the full-length DNA (SEQ ID NO:21) and corresponding deduced amino acid sequence (SEQ ID NO:29) of *Ammonifex degensii* aspartate aminotransferase.

Figure 6 is an illustration of the full-length DNA (SEQ ID NO:22) and corresponding deduced amino acid sequence (SEQ ID NO:30) of *Aquifex* glucosamine:fructose-6-phosphate aminotransferase.

Figure 7 is an illustration of the full-length DNA (SEQ ID NO:23) and corresponding deduced amino acid sequence (SEQ ID NO:31) of *Aquifex* histidinol-phosphate aminotransferase.

Figure 8 is an illustration of the full-length DNA (SEQ ID NO:24) and corresponding deduced amino acid sequence (SEQ ID NO:32) of *Pyrobaculum aerophilum* branched chain aminotransferase.

Figure 9 is a diagramatic illustration of the assay used to assess aminotransferase activity of the proteins using glutamate dehydrogenase.

The term "gene" means the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding region (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons).

A coding sequence is "operably linked to" another coding sequence when RNA polymerase will transcribe the two coding sequences into a single mRNA, which is then translated into a single polypeptide having amino acids derived from both coding sequences. The coding sequences need not be contiguous to one another so long as the expressed sequences ultimately process to produce the desired protein.

"Recombinant" enzymes refer to enzymes produced by recombinant DNA techniques; *i.e.*, produced from cells transformed by an exogenous DNA construct encoding the desired enzyme. "Synthetic" enzymes are those prepared by chemical synthesis.

A DNA "coding sequence of" or a "nucleotide sequence encoding" a particular enzyme, is a DNA sequence which is transcribed and translated into an enzyme when placed under the control of appropriate regulatory sequences.

In accordance with an aspect of the present invention, there are provided isolated nucleic acids (polynucleotides) which encode for the mature enzymes having the deduced amino acid sequences of Figures 1-8 (SEQ ID NOS:17-32).

In accordance with another aspect of the present invention, there are provided isolated polynucleotides encoding the enzymes of the present invention. The deposited material is a mixture of genomic clones comprising DNA encoding an enzyme of the present invention. Each genomic clone comprising the respective DNA has been inserted into a pQE vector (Quiagen, Inc., Chatsworth, CA). The deposit has been deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, USA, on December 13, 1995 and assigned ATCC Deposit No. _____.

The deposit(s) have been made under the terms of the Budapest Treaty on the International Recognition of the deposit of micro-organisms for purposes of patent procedure. The strains will be irrevocably and without restriction or condition released to the public upon the issuance of a patent. These deposits are provided merely as convenience to those of skill in the art and are not an admission that a deposit would be required under 35 U.S.C. §112. The sequences of the polynucleotides contained in the deposited materials, as well as the amino acid sequences of the polypeptides encoded thereby, are controlling in the event of any conflict with any description of sequences herein. A license may be required to make, use or sell the deposited materials, and no such license is hereby granted.

The polynucleotides of this invention were originally recovered from genomic DNA libraries derived from the following organisms:

Aquifex VF5 is a Eubacteria which was isolated in Vulcano, Italy. It is a gram-negative, rod-shaped, strictly chemolithoautotrophic, marine organism which grows

optimally at 85-90°C (T_{max}=95°C) at pH 6.8 in a high salt culture medium with Q as a substrate, and H_2/CO_2+0.5% O_2 in gas phase.

Ammonifex degensii KC4 is a new Eubacaterial organism isolated in Java, Indonesia. This Gram negative chemolithoautotroph has three respiration systems. The bacterium can utilize nitrate, sulfate, and sulfur. The organism grows optimally at 70°C, and pH 7.0, in a low salt culture medium with 0.2% nitrate as a substrate and H_2/CO_2 in gas phase.

Pyrobaculum aerophilium IM2 is a thermophilic sulfur archaea (Crenarchaeota) isolated in Ischia Maronti, Italy. It is a rod-shaped organism that grows optimally at 100°C at pH 7.0 in a low salt culture medium with nitrate, yeast extract, peptone, and O_2 as substrates and N_2/CO_2, O_2 in gas phase.

Accordingly, the polynucleotides and enzymes encoded thereby are identified by the organism from which they were isolated, and are sometimes hereinafter referred to as "VF5/ATA" (Figure 1 and SEQ ID NOS:17 and 25), "VF5/AAB" (Figure 2 and SEQ ID NOS:18 and 26), "VF5/A87A" (Figure 3 and SEQ ID NOS:19 and 27), "VF5/AOA" (Figure 4 and SEQ ID NOS:20 and 28), "KC4/AA" (Figure 5 and SEQ ID NOS:21 and 29), "VF5/GF6PA" (Figure 6 and SEQ ID NOS:22 and 30), "VF5/HPA" (Figure 7 and SEQ ID NOS:23 and 31) and "IM2/BCA" (Figure 8 and SEQ ID NOS:24 and 32).

The polynucleotides and polypeptides of the present invention show identity at the nucleotide and protein level to known genes and proteins encoded thereby as shown in Table 1.

Table 1

Enzyme	Gene w/closest Homology (Organism)	Protein Similarity (%)	Protein Identity (%)	DNA Identity (%)

VF5/ATA	*Bacillus subtilis*	57.5	38.3	50.1
VF5/AAB	*Sulfolobus solfataricus*	62.5	33.0	50.1
VF5/A87A	*Bacillus sphaericus BioA*	67.4	42.9	51
VF5/AOA	*Bacillus subtilis argD*	70.6	48.7	52.0
KC4/AA	*Bacillus YM-2 aspC*	72.6	52.7	52.0
VF5/GF6PA	*Rhizobium Leguminosarum NodM*	66.3	47.7	51.0
VF5/HPA	*Bacillus subtilis HisH/E.coli HisC (same gene)*	55.7	32.6	45.3
IM2/BCA	*E.coli iluE*	63.7	43.6	49.7

All the clones identified in Table 1 encode polypeptides which have transaminase or aminotransferase activity.

One means for isolating the nucleic acid molecules encoding the enzymes of the present invention is to probe a gene library with a natural or artificially designed probe using art recognized procedures (see, for example: Current Protocols in Molecular Biology, Ausubel F.M. *et al.* (EDS.) Green Publishing Company Assoc. and John Wiley Interscience, New York, 1989, 1992). It is appreciated by one skilled in the art that the polynucleotides of SEQ ID NOS:17-24, or fragments thereof (comprising at least 12 contiguous nucleotides), are particularly useful probes. Other particularly useful probes for this purpose are hybridizable fragments of the sequences of SEQ ID NOS:1-9 (*i.e.*, comprising at least 12 contiguous nucleotides).

With respect to nucleic acid sequences which hybridize to specific nucleic acid sequences disclosed herein, hybridization may be carried out under conditions of reduced stringency, medium stringency or even stringent conditions. As an example of oligonucleotide hybridization, a polymer membrane containing immobilized denatured nucleic acids is first prehybridized for 30 minutes at 45°C in a solution consisting of 0.9

M NaCl, 50 mM NaH_2PO_4, pH 7.0, 5.0 mM Na_2EDTA, 0.5% SDS, 10X Denhardt's, and 0.5 mg/mL polyriboadenylic acid. Approximately 2 X 10^7 cpm (specific activity 4-9 X 10^8 cpm/ug) of ^{32}P end-labeled oligonucleotide probe are then added to the solution. After 12-16 hours of incubation, the membrane is washed for 30 minutes at room temperature in 1X SET (150 mM NaCl, 20 mM Tris hydrochloride, pH 7.8, 1 mM Na_2EDTA) containing 0.5% SDS, followed by a 30 minute wash in fresh 1X SET at Tm -10°C (Tm is minus 10°C) for the oligo-nucleotide probe. The membrane is then exposed to auto-radiographic film for detection of hybridization signals.

Stringent conditions means hybridization will occur only if there is at least 90% identity, preferably at least 95% identity and most preferably at least 97% identity between the sequences. *See* J. Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual, 2d Ed.*, Cold Spring Harbor Laboratory (1989) which is hereby incorporated by reference in its entirety.

As used herein, a first DNA (RNA) sequence is at least 70% and preferably at least 80% identical to another DNA (RNA) sequence if there is at least 70% and preferably at least a 80% or 90% identity, respectively, between the bases of the first sequence and the bases of the another sequence, when properly aligned with each other, for example when aligned by BLASTN.

The present invention relates to polynucleotides which differ from the reference polynucleotide such that the changes are silent changes, for example the change does not or the changes do not alter the amino acid sequence encoded by the polynucleotide. The present invention also relates to nucleotide changes which result in amino acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference polynucleotide. In a preferred aspect of the invention these polypeptides retain the same biological action as the polypeptide encoded by the reference polynucleotide.

The polynucleotides of this invention were recovered from genomic gene libraries from the organisms listed in Table 1. Gene libraries were generated in the Lambda ZAP II cloning vector (Stratagene Cloning Systems). Mass excisions were performed on these libraries to generate libraries in the pBluescript phagemid. Libraries were generated and excisions were performed according to the protocols/methods hereinafter described.

The polynucleotides of the present invention may be in the form of RNA or DNA which DNA includes cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single stranded may be the coding strand or non-coding (anti-sense) strand. The coding sequences which encodes the mature enzymes may be identical to the coding sequences shown in Figures 1-8 (SEQ ID NOS:17-24) or may be a different coding sequence which coding sequence, as a result of the redundancy or degeneracy of the genetic code, encodes the same mature enzymes as the DNA of Figures 1-8 (SEQ ID NOS:17-24).

The polynucleotide which encodes for the mature enzyme of Figures 1-8 (SEQ ID NOS:25-32) may include, but is not limited to: only the coding sequence for the mature enzyme; the coding sequence for the mature enzyme and additional coding sequence such as a leader sequence or a proprotein sequence; the coding sequence for the mature enzyme (and optionally additional coding sequence) and non-coding sequence, such as introns or non-coding sequence 5' and/or 3' of the coding sequence for the mature enzyme.

Thus, the term "polynucleotide encoding an enzyme (protein)" encompasses a polynucleotide which includes only coding sequence for the enzyme as well as a polynucleotide which includes additional coding and/or non-coding sequence.

The present invention further relates to variants of the hereinabove described polynucleotides which encode for fragments, analogs and derivatives of the enzymes

having the deduced amino acid sequences of Figures 1-8 (SEQ ID NOS:25-32). The variant of the polynucleotide may be a naturally occurring allelic variant of the polynucleotide or a non-naturally occurring variant of the polynucleotide.

Thus, the present invention includes polynucleotides encoding the same mature enzymes as shown in Figures 1-8 (SEQ ID NOS:17-24) as well as variants of such polynucleotides which variants encode for a fragment, derivative or analog of the enzymes of Figures 1-8 (SEQ ID NOS:17-24). Such nucleotide variants include deletion variants, substitution variants and addition or insertion variants.

As hereinabove indicated, the polynucleotides may have a coding sequence which is a naturally occurring allelic variant of the coding sequences shown in Figures 1-8 (SEQ ID NOS:17-24). As known in the art, an allelic variant is an alternate form of a polynucleotide sequence which may have a substitution, deletion or addition of one or more nucleotides, which does not substantially alter the function of the encoded enzyme. Also, using directed and other evolution strategies, one may make very minor changes in DNA sequence which can result in major changes in function.

Fragments of the full length gene of the present invention may be used as hybridization probes for a cDNA or a genomic library to isolate the full length DNA and to isolate other DNAs which have a high sequence similarity to the gene or similar biological activity. Probes of this type preferably have at least 10, preferably at least 15, and even more preferably at least 30 bases and may contain, for example, at least 50 or more bases. The probe may also be used to identify a DNA clone corresponding to a full length transcript and a genomic clone or clones that contain the complete gene including regulatory and promotor regions, exons and introns. An example of a screen comprises isolating the coding region of the gene by using the known DNA sequence to synthesize an oligonucleotide probe. Labeled oligonucleotides having a sequence complementary or identical to that of the gene or portion of the gene sequences of the

present invention are used to screen a library of genomic DNA to determine which members of the library the probe hybridizes to.

It is also appreciated that such probes can be and are preferably labeled with an analytically detectable reagent to facilitate identification of the probe. Useful reagents include but are not limited to radioactivity, fluorescent dyes or enzymes capable of catalyzing the formation of a detectable product. The probes are thus useful to isolate complementary copies of DNA from other sources or to screen such sources for related sequences.

The present invention further relates to polynucleotides which hybridize to the hereinabove-described sequences if there is at least 70%, preferably at least 90%, and more preferably at least 95% identity between the sequences. The present invention particularly relates to polynucleotides which hybridize under stringent conditions to the hereinabove-described polynucleotides. As herein used, the term "stringent conditions" means hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences. The polynucleotides which hybridize to the hereinabove described polynucleotides in a preferred embodiment encode enzymes which either retain substantially the same biological function or activity as the mature enzyme encoded by the DNA of Figures 1-8 (SEQ ID NOS:17-24).

Alternatively, the polynucleotide may have at least 15 bases, preferably at least 30 bases, and more preferably at least 50 bases which hybridize to any part of a polynucleotide of the present invention and which has an identity thereto, as hereinabove described, and which may or may not retain activity. For example, such polynucleotides may be employed as probes for the polynucleotides of SEQ ID NOS:17-24, for example, for recovery of the polynucleotide or as a diagnostic probe or as a PCR primer.

Thus, the present invention is directed to polynucleotides having at least a 70% identity, preferably at least 90% identity and more preferably at least a 95% identity to a polynucleotide which encodes the enzymes of SEQ ID NOS:25-32 as well as fragments thereof, which fragments have at least 15 bases, preferably at least 30 bases and most preferably at least 50 bases, which fragments are at least 90% identical, preferably at least 95% identical and most preferably at least 97% identical under stringent conditions to any portion of a polynucleotide of the present invention.

The present invention further relates to enzymes which have the deduced amino acid sequences of Figures 1-8 (SEQ ID NOS:17-24) as well as fragments, analogs and derivatives of such enzyme.

The terms "fragment," "derivative" and "analog" when referring to the enzymes of Figures 1-8 (SEQ ID NOS:25-32) means enzymes which retain essentially the same biological function or activity as such enzymes. Thus, an analog includes a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature enzyme.

The enzymes of the present invention may be a recombinant enzyme, a natural enzyme or a synthetic enzyme, preferably a recombinant enzyme.

The fragment, derivative or analog of the enzymes of Figures 1-8 (SEQ ID NOS:25-32) may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature enzyme is fused with another compound, such as a compound to increase the half-life of the enzyme (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature enzyme, such as a leader or secretory sequence or a sequence which is

employed for purification of the mature enzyme or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

The enzymes and polynucleotides of the present invention are preferably provided in an isolated form, and preferably are purified to homogeneity.

The term "isolated" means that the material is removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or enzyme present in a living animal is not isolated, but the same polynucleotide or enzyme, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotides could be part of a vector and/or such polynucleotides or enzymes could be part of a composition, and still be isolated in that such vector or composition is not part of its natural environment.

The enzymes of the present invention include the enzymes of SEQ ID NOS:25-32 (in particular the mature enzyme) as well as enzymes which have at least 70% similarity (preferably at least 70% identity) to the enzymes of SEQ ID NOS:25-32 and more preferably at least 90% similarity (more preferably at least 90% identity) to the enzymes of SEQ ID NOS:25-32 and still more preferably at least 95% similarity (still more preferably at least 95% identity) to the enzymes of SEQ ID NOS:25-32 and also include portions of such enzymes with such portion of the enzyme generally containing at least 30 amino acids and more preferably at least 50 amino acids.

As known in the art "similarity" between two enzymes is determined by comparing the amino acid sequence and its conserved amino acid substitutes of one enzyme to the sequence of a second enzyme.

A variant, *i.e.* a "fragment", "analog" or "derivative" polypeptide, and reference polypeptide may differ in amino acid sequence by one or more substitutions, additions, deletions, fusions and truncations, which may be present in any combination.

Among preferred variants are those that vary from a reference by conservative amino acid substitutions. Such substitutions are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe, Tyr.

Most highly preferred are variants which retain the same biological function and activity as the reference polypeptide from which it varies.

Fragments or portions of the enzymes of the present invention may be employed for producing the corresponding full-length enzyme by peptide synthesis; therefore, the fragments may be employed as intermediates for producing the full-length enzymes. Fragments or portions of the polynucleotides of the present invention may be used to synthesize full-length polynucleotides of the present invention.

The present invention also relates to vectors which include polynucleotides of the present invention, host cells which are genetically engineered with vectors of the invention and the production of enzymes of the invention by recombinant techniques.

Host cells are genetically engineered (transduced or transformed or transfected) with the vectors of this invention which may be, for example, a cloning vector such as an expression vector. The vector may be, for example, in the form of a plasmid, a phage, *etc.* The engineered host cells can be cultured in conventional nutrient media

modified as appropriate for activating promoters, selecting transformants or amplifying the genes of the present invention. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

The polynucleotides of the present invention may be employed for producing enzymes by recombinant techniques. Thus, for example, the polynucleotide may be included in any one of a variety of expression vectors for expressing an enzyme. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences, *e.g.*, derivatives of SV40; bacterial plasmids; phage DNA; baculovirus; yeast plasmids; vectors derived from combinations of plasmids and phage DNA, viral DNA such as vaccinia, adenovirus, fowl pox virus, and pseudorabies. However, any other vector may be used as long as it is replicable and viable in the host.

The appropriate DNA sequence may be inserted into the vector by a variety of procedures. In general, the DNA sequence is inserted into an appropriate restriction endonuclease site(s) by procedures known in the art. Such procedures and others are deemed to be within the scope of those skilled in the art.

The DNA sequence in the expression vector is operatively linked to an appropriate expression control sequence(s) (promoter) to direct mRNA synthesis. As representative examples of such promoters, there may be mentioned: LTR or SV40 promoter, the *E. coli. lac* or *trp*, the phage lambda P_L promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or their viruses. The expression vector also contains a ribosome binding site for translation initiation and a transcription terminator. The vector may also include appropriate sequences for amplifying expression.

In addition, the expression vectors preferably contain one or more selectable marker genes to provide a phenotypic trait for selection of transformed host cells such

as dihydrofolate reductase or neomycin resistance for eukaryotic cell culture, or such as tetracycline or ampicillin resistance in *E. coli*.

The vector containing the appropriate DNA sequence as hereinabove described, as well as an appropriate promoter or control sequence, may be employed to transform an appropriate host to permit the host to express the protein.

As representative examples of appropriate hosts, there may be mentioned: bacterial cells, such as *E. coli, Streptomyces, Bacillus subtilis*; fungal cells, such as yeast; insect cells such as *Drosophila S2* and *Spodoptera Sf9*; animal cells such as CHO, COS or Bowes melanoma; adenoviruses; plant cells, *etc.* The selection of an appropriate host is deemed to be within the scope of those skilled in the art from the teachings herein.

More particularly, the present invention also includes recombinant constructs comprising one or more of the sequences as broadly described above. The constructs comprise a vector, such as a plasmid or viral vector, into which a sequence of the invention has been inserted, in a forward or reverse orientation. In a preferred aspect of this embodiment, the construct further comprises regulatory sequences, including, for example, a promoter, operably linked to the sequence. Large numbers of suitable vectors and promoters are known to those of skill in the art, and are commercially available. The following vectors are provided by way of example; Bacterial: pQE70, pQE60, pQE-9 (Qiagen), pBluescript II KS, ptrc99a, pKK223-3, pDR540, pRIT2T (Pharmacia); Eukaryotic: pXT1, pSG5 (Stratagene) pSVK3, pBPV, pMSG, pSVL SV40 (Pharmacia). However, any other plasmid or vector may be used as long as they are replicable and viable in the host.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters

include lacI, lacZ, T3, T7, gpt, lambda P_R, P_L and trp. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art.

In a further embodiment, the present invention relates to host cells containing the above-described constructs. The host cell can be a higher eukaryotic cell, such as a mammalian cell, or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-Dextran mediated transfection, or electroporation (Davis, L., Dibner, M., Battey, I., *Basic Methods in Molecular Biology*, (1986)).

The constructs in host cells can be used in a conventional manner to produce the gene product encoded by the recombinant sequence. Alternatively, the enzymes of the invention can be synthetically produced by conventional peptide synthesizers.

Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook *et al., Molecular Cloning: A Laboratory Manual, Second Edition*, Cold Spring Harbor, N.Y., (1989), the disclosure of which is hereby incorporated by reference.

Transcription of the DNA encoding the enzymes of the present invention by higher eukaryotes is increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp that act on a promoter to increase its transcription. Examples include the SV40 enhancer on the late side of the replication origin bp 100 to 270, a cytomegalovirus early promoter enhancer,

the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, *e.g.*, the ampicillin resistance gene of *E. coli* and *S. cerevisiae* TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), α-factor, acid phosphatase, or heat shock proteins, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated enzyme. Optionally, the heterologous sequence can encode a fusion enzyme including an N-terminal identification peptide imparting desired characteristics, *e.g.*, stabilization or simplified purification of expressed recombinant product.

Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and to, if desirable, provide amplification within the host. Suitable prokaryotic hosts for transformation include *E. coli, Bacillus subtilis, Salmonella typhimurium* and various species within the genera Pseudomonas, Streptomyces, and Staphylococcus, although others may also be employed as a matter of choice.

As a representative but nonlimiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example,

pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and pGEM1 (Promega Biotec, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed.

Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is induced by appropriate means (*e.g.*, temperature shift or chemical induction) and cells are cultured for an additional period.

Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents, such methods are well known to those skilled in the art.

Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts, described by Gluzman, *Cell, 23*:175 (1981), and other cell lines capable of expressing a compatible vector, for example, the C127, 3T3, CHO, HeLa and BHK cell lines. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and enhancer, and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 splice, and polyadenylation sites may be used to provide the required nontranscribed genetic elements.

The enzyme can be recovered and purified from recombinant cell cultures by methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic

interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps.

The enzymes of the present invention may be a naturally purified product, or a product of chemical synthetic procedures, or produced by recombinant techniques from a prokaryotic or eukaryotic host (for example, by bacterial, yeast, higher plant, insect and mammalian cells in culture). Depending upon the host employed in a recombinant production procedure, the enzymes of the present invention may be glycosylated or may be non-glycosylated. Enzymes of the invention may or may not also include an initial methionine amino acid residue.

Transaminases are a group of key enzymes in the metabolism of amino acids and amino sugars and are found in all organisms from microbes to mammals. In the transamination reaction, an amino group is transferred from an amino acid to an α-keto acid. Pyridoxal phosphate is required as a co-factor to mediate the transfer of the amino group without liberation of ammonia.

Amino acids currently have applications as additives to aminal feed, human nutritional supplements, components in infusion solutions, and synthetic intermediates for manufacture of pharmaceuticals and agricultural products. For example, L-glutamic acid is best known as a flavor enhancer for human food. L-lysine and L-methionine are large volume additives to animal feed and human supplements. L-tryptophan and L-threonine have similar potential applications. L-phenylalanine and L-aspartic acid have very important market potential as key components in the manufacture of the low-calorie sweetener aspartame, and other promising low-calorie sweeteners have compositions containing certain amino acids as well. Infusion solutions require a large range of amino acids including those essential ones in human diets.

Transaminases are highly stereoselective, and most use L-amino acids as substrates. Using the approach disclosed in a commonly assigned, copending provisional application Serial No. 60/008,316, filed on December 7, 1995 and entitled "Combinatorial Enzyme Development," the disclosure of which is incorporated herein by reference in its entirety, one can convert the transaminases of the invention to use D-amino acids as substrates. Such conversion makes possible a broader array of transaminase applications. For instance, D-valine can be used in the manufacture of synthetic pyrethroids. D-phenylglycine and its derivatives can be useful as components of β-lactam antibiotics. Further, the thermostable transaminases have superior stability at higher temperatures and in organic solvents. Thus, they are better suited to utilize either L- and/or D-amino acids for production of optically pure chiral compounds used in pharmaceutical, agricultural, and other chemical manufactures.

There are a number of reasons to employ transaminases in industrial-scale production of amino acids and their derivatives.

1) Transaminases can catalyze stereoselective synthesis of D- or L-amino acids from their corresponding α-keto acids. Therefore no L- or D-isomers are produced, and no resolution is required.

2) Transaminases have uniformly high catalytic rates, capable of converting up to 400 μmoles of substrates per minute per mg enzyme.

3) Many required α-keto acids can be conveniently prepared by chemical synthesis at low cost.

4) The capital investment for an immobilized enzyme process using transaminases is much lower than for a large scale fermentation process, and productivity of the bioreactor is often an order of magnitude higher.

5) The technology is generally applicable to a broad range of D- or L-amino acids because transaminases exist with varying specificities. Such broad scope allows a number of different L- or D-amino acids to be produced with the same equipment and often the same biocatalyst.

Antibodies generated against the enzymes corresponding to a sequence of the present invention can be obtained by direct injection of the enzymes into an animal or by administering the enzymes to an animal, preferably a nonhuman. The antibody so obtained will then bind the enzymes itself. In this manner, even a sequence encoding only a fragment of the enzymes can be used to generate antibodies binding the whole native enzymes. Such antibodies can then be used to isolate the enzyme from cells expressing that enzyme.

For preparation of monoclonal antibodies, any technique which provides antibodies produced by continuous cell line cultures can be used. Examples include the hybridoma technique (Kohler and Milstein, *Nature, 256*:495-497, 1975), the trioma technique, the human B-cell hybridoma technique (Kozbor *et al.*, *Immunology Today 4*:72, 1983), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole *et al.*, in *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96, 1985).

Techniques described for the production of single chain antibodies (U.S. Patent 4,946,778) can be adapted to produce single chain antibodies to immunogenic enzyme products of this invention. Also, transgenic mice may be used to express humanized antibodies to immunogenic enzyme products of this invention.

Antibodies generated against an enzyme of the present invention may be used in screening for similar enzymes from other organisms and samples. Such screening techniques are known in the art, for example, one such screening assay is described in Sambrook and Maniatis, Molecular Cloning: A Laboratory Manual (2d Ed.), vol.

2:Section 8.49, Cold Spring Harbor Laboratory, 1989, which is hereby incorporated by reference in its entirety.

The present invention will be further described with reference to the following examples; however, it is to be understood that the present invention is not limited to such examples. All parts or amounts, unless otherwise specified, are by weight.

In order to facilitate understanding of the following examples certain frequently occurring methods and/or terms will be described.

"Plasmids" are designated by a lower case "p" preceded and/or followed by capital letters and/or numbers. The starting plasmids herein are either commercially available, publicly available on an unrestricted basis, or can be constructed from available plasmids in accord with published procedures. In addition, equivalent plasmids to those described are known in the art and will be apparent to the ordinarily skilled artisan.

"Digestion" of DNA refers to catalytic cleavage of the DNA with a restriction enzyme that acts only at certain sequences in the DNA. The various restriction enzymes used herein are commercially available and their reaction conditions, cofactors and other requirements were used as would be known to the ordinarily skilled artisan. For analytical purposes, typically 1 μg of plasmid or DNA fragment is used with about 2 units of enzyme in about 20 μl of buffer solution. For the purpose of isolating DNA fragments for plasmid construction, typically 5 to 50 μg of DNA are digested with 20 to 250 units of enzyme in a larger volume. Appropriate buffers and substrate amounts for particular restriction enzymes are specified by the manufacturer. Incubation times of about 1 hour at 37°C are ordinarily used, but may vary in accordance with the supplier's instructions. After digestion the reaction is electrophoresed directly on a polyacrylamide gel to isolate the desired fragment.

Size separation of the cleaved fragments is performed using 8 percent polyacrylamide gel described by Goeddel *et al.*, *Nucleic Acids Res.*, *8*:4057 (1980).

"Oligonucleotides" refers to either a single stranded polydeoxynucleotide or two complementary polydeoxynucleotide strands which may be chemically synthesized. Such synthetic oligonucleotides have no 5' phosphate and thus will not ligate to another oligonucleotide without adding a phosphate with an ATP in the presence of a kinase. A synthetic oligonucleotide will ligate to a fragment that has not been dephosphorylated.

"Ligation" refers to the process of forming phosphodiester bonds between two double stranded nucleic acid fragments (Maniatis, T., *et al.*, *Id.*, p. 146). Unless otherwise provided, ligation may be accomplished using known buffers and conditions with 10 units of T4 DNA ligase ("ligase") per 0.5 μg of approximately equimolar amounts of the DNA fragments to be ligated.

Unless otherwise stated, transformation was performed as described in Sambrook and Maniatis, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, 1989.

Example 1

Bacterial Expression and Purification of Transaminases and Aminotransferases

DNA encoding the enzymes of the present invention, SEQ ID NOS:25 through 32, were initially amplified from a pBluescript vector containing the DNA by the PCR technique using the primers noted herein. The amplified sequences were then inserted into the respective PQE vector listed beneath the primer sequences, and the enzyme was expressed according to the protocols set forth herein. The genomic DNA has also been used as a template for the PCR amplification, *i.e.*, once a positive clone has been identified and primer sequences determined using the cDNA, it was then possible to return to the genomic DNA and directly amplify the desired sequence(s) there. The 5' and 3' primer sequences and the vector for the respective genes are as follows:

***Aquifex* Aspartate Transaminase A**

aspa501 5′ CCGAGAATTCATTAAAGAGGAGAAATTAACTATGATTGAAGACCCTATGGAC (SEQ. ID NO:1)

aspa301 3′ CGAAGATCTTTAGCACTTCTCTCAGGTTC (SEQ. ID NO:2)

vector: pQET1

***Aquifex* Aspartate Aminotransferase B**

aspb501 5′ CCGAGAATTCATTAAAGAGGAGAAATTAACTATGGACAGGCTTGAAAAAGTA (SEQ ID NO:3)

aspb301 3′ CGGAAGATCTTCAGCTAAGCTTCTCTAAGAA (SEQ ID NO:4)

vector: pQET1

***Aquifex* Adenosyl-8-amino-7-oxononanoate Aminotransferase**

ameth501 5′ CCGACAATTGATTAAAGAGGAGAAATTAACTATGTGGGAATTAGACCCTAAA (SEQ ID NO:5)

ameth301 3′ CGGAGGATCCCTACACCTCTTTTTCAAGCT (SEQ ID NO:6)

vector: pQET12

***Aquifex* Acetylornithine Aminotransferase**

aorn 501 5′ CCGACAATTGATTAAAGAGGAGAAATTAACTATGACATACTTAATGAACAAT (SEQ ID NO:7)

aorn 301 3′ CGGAAGATCTTTATGAGAAGTCCCTTTCAAG (SEQ ID NO:8)

vector: pQET12

***Ammonifex degensii* Aspartate Aminotransferase**

adasp 501 5′ CCGAGAATTCATTAAAGAGGAGAAATTAACTATGCGGAAACTGGCCGAGCGG (SEQ ID NO:9)

adasp 301 3′ CGGAGGATCCTTAAAGTGCCGCTTCGATCAA (SEQ ID NO:10)

vector: pQET12

***Aquifex* Glucosamine:Fructose-6-phosphate Aminotransferase**

glut 501 5′ CCGACAATTGATTAAAGAGGAGAAATTAACTATGTGCGGGATAGTCGGATAC (SEQ ID NO:11)

glut 301 3′ CGGAAGATCTTTATTCCACCGTGACCGTTTT (SEQ ID NO:12)

vector: pQET1

***Aquifex* Histadine-phosphate Aminotransferase**

his 501 5′ CCGACAATTGATTAAAGAGGAGAAATTAACTATGATACCCCAGAGGATTAAG (SEQ ID NO:13)
his 301 3′ CGGAAGATCTTTAAAGAGAGCTTGAAAGGGA (SEQ ID NO:14)
vector: pQET1

***Pyrobacullum aerophilum* Branched Chain Aminotransferase**

bcat 501 5′ CCGAGAATTCATTAAAGAGGAGAAATTAACTATGAAGCCGTACGCTAAATAT (SEQ ID NO:15)
bcat 301 3′ CGGAAGATCTCTAATACACAGGAGTGATCCA (SEQ ID NO:16)
vector: pQET1

The restriction enzyme sites indicated correspond to the restriction enzyme sites on the bacterial expression vector indicated for the respective gene (Qiagen, Inc. Chatsworth, CA). The pQE vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter operator (P/O), a ribosome binding site (RBS), a 6-His tag and restriction enzyme sites.

The pQE vector was digested with the restriction enzymes indicated. The amplified sequences were ligated into the respective pQE vector and inserted in frame with the sequence encoding for the RBS. The ligation mixture was then used to transform the *E. coli* strain M15/pREP4 (Qiagen, Inc.) by electroporation. M15/pREP4 contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants were identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies were selected. Plasmid DNA was isolated and confirmed by restriction analysis. Clones containing the desired constructs were grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture was used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells were grown to an optical density 600 ($O.D._{600}$) of between 0.4 and 0.6. IPTG ("Isopropyl-B-D-thiogalacto pyranoside") was then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression. Cells were grown an extra 3 to 4 hours. Cells were then harvested by centrifugation.

The primer sequences set out above may also be employed to isolate the target gene from the deposited material by hybridization techniques described above.

Example 2

Isolation of a Selected Clone from the Deposited Genomic Clones

The two oligonucleotide primers corresponding to the gene of interest are used to amplify the gene from the deposited material. A polymerase chain reaction is carried out in 25 μl of reaction mixture with 0.1 μg of the DNA of the gene of interest. The reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 1.25 Unit of Taq polymerase. Thirty cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with the Perkin-Elmer Cetus 9600 thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the gene of interest by subcloning and sequencing the DNA product.

Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, within the scope of the appended claims, the invention may be practiced otherwise than as particularly described.

What Is Claimed Is:

1. An isolated polynucleotide encoding an enzyme with aminotransferase activity and which is at least 70% identical to a member selected from the group consisting of:
   a) SEQ ID NOS:25-32;
   b) SEQ ID NOS:25-32 wherein T can also be U;
   c) nucleic acid sequences complementary to a) and b); and
   d) fragments of a), b) or c) that are at least 15 bases in length and that hybridize to DNA which encodes the amino acid sequences of SEQ ID NOS:25-32 under moderate to highly stringent conditions.

2. The polynucleotide of claim 1, wherein the polynucleotide is DNA.

3. The polynucleotide of claim 1, wherein the polynucleotide is RNA.

4. The polynucleotide of claim 2 which encodes the enzyme of SEQ ID NO:25.

5. The polynucleotide of claim 2 which encodes the enzyme of SEQ ID NO:26.

6. The polynucleotide of claim 2 which encodes the enzyme of SEQ ID NO:27.

7. The polynucleotide of claim 2 which encodes the enzyme of SEQ ID NO:28.

8. The polynucleotide of claim 2 which encodes the enzyme of SEQ ID NO:29.

9. The polynucleotide of claim 2 which encodes the enzyme of SEQ ID NO:30.

10. The polynucleotide of claim 2 which encodes the enzyme of SEQ ID NO:31.

11. The polynucleotide of claim 2 which encodes the enzyme of SEQ ID NO:32.

12. The polynucleotides of claim 1 comprising the sequences as set forth in SEQ ID NOS:17-24.

13. A vector comprising the DNA of claim 2.

14. A host cell comprising the vector of claim 13.

15. An enzyme wherein the enzyme is an aminotransferase and is selected from the group consisting of:

a) an enzyme comprising an amino acid sequence that is at least 70% identical to the amino acid sequences set forth in SEQ ID NOS:25-32; and

b) an enzyme comprising at least 30 consecutive amino acid residues homologous with an enzyme of a).

16. A protein encoding a polypeptide of claim 15.

17. A nucleic acid probe comprising an oligonucleotide from about 10 to 50 nucleotides in length and having an area of nucleotides that is at least 70% complementary to a nucleic acid target region of a nucleic acid encoding an amino acid sequence selected from the group consisting of SEQ ID NOS:25-32 and which hybridizes to the nucleic acid target region under moderate to highly stringent conditions to form a detectable target:probe duplex.

18. The probe of claim 17, wherein the oligonucleotide is DNA.

19. The probe of claim 17, wherein the oligonucleotide comprises a sequence which is at least 90% complementary to the nucleic acid target region.

20. The probe of claim 17, wherein the oligonucleotide comprises a sequence which is 95% complementary to the nucleic acid target region.

21. The probe of claim 17, wherein the oligonucleotide comprises a sequence which is 100% complementary to the nucleic acid target region.

22. The probe of claim 17, wherein the oligonucleotide is 15-50 bases in length.

23. The probe of claim 17, wherein the probe further comprises a detectable isotopic label.

24. The probe of claim 17, wherein the probe further comprises a detectable non-isotopic label selected from the group consisting of a fluorescent molecule, a chemiluminescent molecule, an enzyme, a cofactor, an enzyme substrate, and a hapten.

ABSTRACT

Thermostable transaminase and aminotransferase enzymes derived from various *ammonifex, aquifex* and *pyrobaculum* organisms are disclosed. The enzymes are produced from native or recombinant host cells and can be utilized in the pharmaceutical, agricultural and other industries.

```
ATG ATT GAA GAC CCT ATG GAC TGG GCT TTT CCG AGG ATA AAG AGA CTG          48
Met Ile Glu Asp Pro Met Asp Trp Ala Phe Pro Arg Ile Lys Arg Leu
                5                  10                  15

CCT CAG TAT GTC TTC TCT CTC GTT AAC GAA CTC AAG TAC AAG CTA AGG          96
Pro Gln Tyr Val Phe Ser Leu Val Asn Glu Leu Lys Tyr Lys Leu Arg
            20                  25                  30

CGT GAA GGC GAA GAT GTA GTG GAT CTT GGT ATG GGC AAT CCT AAC ATG         144
Arg Glu Gly Glu Asp Val Val Asp Leu Gly Met Gly Asn Pro Asn Met
        35                  40                  45

CCT CCA GCA AAG CAC ATA ATA GAT AAA CTC TGC GAA GTG GCT CAA AAG         192
Pro Pro Ala Lys His Ile Ile Asp Lys Leu Cys Glu Val Ala Gln Lys
    50                  55                  60

CCG AAC GTT CAC GGA TAT TCT GCG TCA AGG GGC ATA CCA AGA CTG AGA         240
Pro Asn Val His Gly Tyr Ser Ala Ser Arg Gly Ile Pro Arg Leu Arg
65                  70                  75                  80

AAG GCT ATA TGT AAC TTC TAC GAA GAA AGG TAC GGA GTG AAA CTC GAC         288
Lys Ala Ile Cys Asn Phe Tyr Glu Glu Arg Tyr Gly Val Lys Leu Asp
                85                  90                  95

CCT GAG AGG GAG GCT ATA CTA ACA ATC GGT GCA AAG GAA GGG TAT TCT         336
Pro Glu Arg Glu Ala Ile Leu Thr Ile Gly Ala Lys Glu Gly Tyr Ser
            100                 105                 110

CAT TTG ATG CTT GCG ATG ATA TCT CCG GGT GAT ACG GTA ATA GTT CCT         384
His Leu Met Leu Ala Met Ile Ser Pro Gly Asp Thr Val Ile Val Pro
        115                 120                 125

AAT CCC ACC TAT CCT ATT CAC TAT TAC GCT CCC ATA ATT GCA GGA GGG         432
Asn Pro Thr Tyr Pro Ile His Tyr Tyr Ala Pro Ile Ile Ala Gly Gly
    130                 135                 140

GAA GTT CAC TCA ATA CCC CTT AAC TTC TCG GAC GAT CAA GAT CAT CAG         480
Glu Val His Ser Ile Pro Leu Asn Phe Ser Asp Asp Gln Asp His Gln
145                 150                 155                 160

GAA GAG TTT TTA AGG AGG CTT TAC GAG ATA GTA AAA ACC GCG ATG CCA         528
Glu Glu Phe Leu Arg Arg Leu Tyr Glu Ile Val Lys Thr Ala Met Pro
                165                 170                 175

AAA CCC AAG GCT GTC GTC ATA AGC TTT CCT CAC AAT CCA ACG ACC ATA         576
Lys Pro Lys Ala Val Val Ile Ser Phe Pro His Asn Pro Thr Thr Ile
            180                 185                 190

ACG GTA GAA AAG GAC TTT TTT AAA GAA ATA GTT AAG TTT GCA AAG GAA         624
Thr Val Glu Lys Asp Phe Phe Lys Glu Ile Val Lys Phe Ala Lys Glu
        195                 200                 205

CAC GGT CTC TGG ATA ATA CAC GAT TTT GCG TAT GCG GAT ATA GCC TTT         672
His Gly Leu Trp Ile Ile His Asp Phe Ala Tyr Ala Asp Ile Ala Phe
    210                 215                 220

GAC GGT TAC AAG CCC CCC TCA ATA CTC GAA ATA GAA GGT GCT AAA GAC         720
Asp Gly Tyr Lys Pro Pro Ser Ile Leu Glu Ile Glu Gly Ala Lys Asp
225                 230                 235                 240
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FIG. 1A

```
GTT GCG GTT GAG CTC TAC TCC ATG TCA AAG GGC TTT TCA ATG GCG GGC          768
Val Ala Val Glu Leu Tyr Ser Met Ser Lys Gly Phe Ser Met Ala Gly
                245                 250                 255

TGG AGG GTA GCC TTT GTC GTT GGA AAC GAA ATA CTC ATA AAA AAC CTT          816
Trp Arg Val Ala Phe Val Val Gly Asn Glu Ile Leu Ile Lys Asn Leu
            260                 265                 270

GCA CAC CTC AAA AGC TAC TTG GAT TAC GGT ATA TTT ACT CCC ATA CAG          864
Ala His Leu Lys Ser Tyr Leu Asp Tyr Gly Ile Phe Thr Pro Ile Gln
        275                 280                 285

GTG GCC TCT ATT ATC GCA TTA GAG AGC CCC TAC GAA ATC GTG GAA AAA          912
Val Ala Ser Ile Ile Ala Leu Glu Ser Pro Tyr Glu Ile Val Glu Lys
    290                 295                 300

ACC GCA AAG GTT TAC CAA AAA AGA AGA GAC GTT CTG GTG GAA GGG TTA          960
Thr Ala Lys Val Tyr Gln Lys Arg Arg Asp Val Leu Val Glu Gly Leu
305                 310                 315                 320

AAC AGG CTC GGC TGG AAA GTA AAA AAA CCT AAG GCT ACC ATG TTC GTC         1008
Asn Arg Leu Gly Trp Lys Val Lys Lys Pro Lys Ala Thr Met Phe Val
                325                 330                 335

TGG GCA AAG ATT CCC GAA TGG ATA AAT ATG AAC TCT CTG GAC TTT TCC         1056
Trp Ala Lys Ile Pro Glu Trp Ile Asn Met Asn Ser Leu Asp Phe Ser
            340                 345                 350

TTG TTC CTC CTA AAA GAG GCG AAG GTT GCG GTA TCC CCG GGT GTG GGC         1104
Leu Phe Leu Leu Lys Glu Ala Lys Val Ala Val Ser Pro Gly Val Gly
        355                 360                 365

TTT GGT CAG TAC GGA GAG GGG TAC GTA AGG TTT GCA CTT GTA GAA AAT         1152
Phe Gly Gln Tyr Gly Glu Gly Tyr Val Arg Phe Ala Leu Val Glu Asn
    370                 375                 380

GAA CAC AGG ATC AGA CAG GCT ATA AGG GGA ATA AGG AAA GCC TTC AGA         1200
Glu His Arg Ile Arg Gln Ala Ile Arg Gly Ile Arg Lys Ala Phe Arg
385                 390                 395                 400

AAA CTC CAG AAG GAG AGG AAA CTT GAA CCT GAG AGA AGT GCT TAA             1245
Lys Leu Gln Lys Glu Arg Lys Leu Glu Pro Glu Arg Ser Ala End
                405                 410                 414
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FIG. 1B

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ATG GAC AGG CTT GAA AAA GTA TCA CCC TTC ATA GTA ATG GAT ATC CTA          48
Met Asp Arg Leu Glu Lys Val Ser Pro Phe Ile Val Met Asp Ile Leu
                5                  10                  15

GCT CAG GCC CAG AAG TAC GAA GAC GTA GTA CAC ATG GAG ATA GGA GAG          96
Ala Gln Ala Gln Lys Tyr Glu Asp Val Val His Met Glu Ile Gly Glu
            20                  25                  30

CCC GAT TTA GAA CCG TCT CCC AAG GTA ATG GAA GCT CTG GAA CGT GCG         144
Pro Asp Leu Glu Pro Ser Pro Lys Val Met Glu Ala Leu Glu Arg Ala
        35                  40                  45

GTG AAG GAA AAG ACG TTC TTC TAC ACC CCT GCT CTG GGA CTC TGG GAA         192
Val Lys Glu Lys Thr Phe Phe Tyr Thr Pro Ala Leu Gly Leu Trp Glu
    50                  55                  60

CTC AGG GAA AGG ATA TCG GAG TTT TAC AGG AAA AAG TAC AGC GTT GAA         240
Leu Arg Glu Arg Ile Ser Glu Phe Tyr Arg Lys Lys Tyr Ser Val Glu
65                  70                  75                  80

GTT TCT CCA GAG AGA GTC ATC GTA ACT ACC GGA ACT TCG GGA GCG TTT         288
Val Ser Pro Glu Arg Val Ile Val Thr Thr Gly Thr Ser Gly Ala Phe
                85                  90                  95

CTC GTA GCC TAC GCC GTA ACA CTA AAT GCG GGA GAG AAG ATA ATC CTC         336
Leu Val Ala Tyr Ala Val Thr Leu Asn Ala Gly Glu Lys Ile Ile Leu
            100                 105                 110

CCA GAC CCC TCT TAC CCC TGT TAC AAA AAC TTT GCC TAC CTC TTA GAC         384
Pro Asp Pro Ser Tyr Pro Cys Tyr Lys Asn Phe Ala Tyr Leu Leu Asp
        115                 120                 125

GCT CAG CCG GTT TTC GTA AAC GTT GAC AAG GAA ACG AAT TAC GAA GTA         432
Ala Gln Pro Val Phe Val Asn Val Asp Lys Glu Thr Asn Tyr Glu Val
    130                 135                 140

AGG AAA GAG ATG ATA GAA GAC ATT GAT GCG AAA GCC CTT CAC ATT TCC         480
Arg Lys Glu Met Ile Glu Asp Ile Asp Ala Lys Ala Leu His Ile Ser
145                 150                 155                 160

TCG CCT CAA AAC CCT ACG GGC ACA CTC TAC TCA CCT GAA ACC CTG AAG         528
Ser Pro Gln Asn Pro Thr Gly Thr Leu Tyr Ser Pro Glu Thr Leu Lys
                165                 170                 175

GAA CTT GCG GAG TAC TGC GAA GAG AAG GGT ATG TAC TTC ATA TCC GAC         576
Glu Leu Ala Glu Tyr Cys Glu Glu Lys Gly Met Tyr Phe Ile Ser Asp
            180                 185                 190

GAG ATT TAC CAC GGA CTC GTT TAC GAA GGT AGG GAG CAC ACA GCA CTT         624
Glu Ile Tyr His Gly Leu Val Tyr Glu Gly Arg Glu His Thr Ala Leu
        195                 200                 205

GAG TTC TCT GAC AGG GCT ATT GTC ATA AAC GGG TTT TCT AAG TAC TTC         672
Glu Phe Ser Asp Arg Ala Ile Val Ile Asn Gly Phe Ser Lys Tyr Phe
    210                 215                 220

TGT ATG CCA GGT TTC AGG ATA GGG TGG ATG ATA GTT CCG GAA GAA CTC         720
Cys Met Pro Gly Phe Arg Ile Gly Trp Met Ile Val Pro Glu Glu Leu
225                 230                 235                 240
```

FIG. 2A

```
GTG AGA AAG GCG GAA ATA GTA ATT CAG AAC GTA TTT ATA TCT GCC CCG          768
Val Arg Lys Ala Glu Ile Val Ile Gln Asn Val Phe Ile Ser Ala Pro
                245                 250                 255

ACG CTC AGT CAG TAC GCC GCC CTT GAG GCT TTT GAT TAC GAG TAT TTG          816
Thr Leu Ser Gln Tyr Ala Ala Leu Glu Ala Phe Asp Tyr Glu Tyr Leu
            260                 265                 270

GAG AAG GTA AGA AAA ACC TTT GAA GAG AGG AGG AAC TTC CTT TAT GGG          864
Glu Lys Val Arg Lys Thr Phe Glu Glu Arg Arg Asn Phe Leu Tyr Gly
        275                 280                 285

GAA CTG AAA AAA CTC TTC AAG ATA GAC GCG AAA CCT CAG GGA GCT TTT          912
Glu Leu Lys Lys Leu Phe Lys Ile Asp Ala Lys Pro Gln Gly Ala Phe
    290                 295                 300

TAC GTA TGG GCA AAC ATA AGT GAT TAC TCC ACA GAT AGC TAC GAA TTT          960
Tyr Val Trp Ala Asn Ile Ser Asp Tyr Ser Thr Asp Ser Tyr Glu Phe
305                 310                 315                 320

GCT TTA AAA CTT TTA AGG GAG GCG AGG GTG GCG GTA ACG CCC GGG GTG         1008
Ala Leu Lys Leu Leu Arg Glu Ala Arg Val Ala Val Thr Pro Gly Val
                325                 330                 335

GAC TTT GGA AAA AAC AAA ACG AAG GAG TAT ATA AGG TTT GCT TAT ACG         1056
Asp Phe Gly Lys Asn Lys Thr Lys Glu Tyr Ile Arg Phe Ala Tyr Thr
            340                 345                 350

AGA AAG ATA GAA GAA CTT AAG GAG GGC GTT GAA AGG ATA AAG AAG TTC         1104
Arg Lys Ile Glu Glu Leu Lys Glu Gly Val Glu Arg Ile Lys Lys Phe
        355                 360                 365

TTA GAG AAG CTT AGC TGA                                                 1122
Leu Glu Lys Leu Ser End
    370
```

FIG. 2B

```
ATG TGG GAA TTA GAC CCT AAA ACG CTC GAA AAG TGG GAC AAG GAG TAC          48
Met Trp Glu Leu Asp Pro Lys Thr Leu Glu Lys Trp Asp Lys Glu Tyr
                5                  10                  15

TTC TGG CAT CCA TTT ACC CAG ATG AAA GTC TAC AGA GAA GAA GAA AAC          96
Phe Trp His Pro Phe Thr Gln Met Lys Val Tyr Arg Glu Glu Glu Asn
            20                  25                  30

CTG ATA TTT GAA CGC GGA GAA GGC GTT TAC CTG TGG GAC ATA TAC GGC         144
Leu Ile Phe Glu Arg Gly Glu Gly Val Tyr Leu Trp Asp Ile Tyr Gly
        35                  40                  45

AGG AAG TAT ATA GAT GCC ATA TCT TCC CTC TGG TGC AAC GTC CAC GGA         192
Arg Lys Tyr Ile Asp Ala Ile Ser Ser Leu Trp Cys Asn Val His Gly
    50                  55                  60

CAT AAC CAC CCT AAA CTG AAC AAC GCA GTT ATG AAA CAG CTC TGT AAG         240
His Asn His Pro Lys Leu Asn Asn Ala Val Met Lys Gln Leu Cys Lys
65                  70                  75                  80

GTA GCT CAC ACA ACT ACT CTG GGA AGT TCC AAC GTT CCC GCC ATA CTC         288
Val Ala His Thr Thr Thr Leu Gly Ser Ser Asn Val Pro Ala Ile Leu
                85                  90                  95

CTT GCA AAG AAG CTT GTA GAA ATT TCT CCT GAA GGA TTA AAC AAG GTC         336
Leu Ala Lys Lys Leu Val Glu Ile Ser Pro Glu Gly Leu Asn Lys Val
            100                 105                 110

TTT TAC TCC GAA GAC GGT GCG GAA GCA GTA GAG ATA GCG ATA AAG ATG         384
Phe Tyr Ser Glu Asp Gly Ala Glu Ala Val Glu Ile Ala Ile Lys Met
        115                 120                 125

GCT TAT CAC TAC TGG AAG AAC AAG GGA GTT AAA GGG AAA AAC GTT TTC         432
Ala Tyr His Tyr Trp Lys Asn Lys Gly Val Lys Gly Lys Asn Val Phe
    130                 135                 140

ATA ACG CTT TCC GAA GCC TAC CAC GGG GAT ACT GTA GGA GCG GTT AGC         480
Ile Thr Leu Ser Glu Ala Tyr His Gly Asp Thr Val Gly Ala Val Ser
145                 150                 155                 160

GTA GGG GGT ATA GAA CTC TTC CAC GGA ACT TAT AAA GAT CTC CTT TTC         528
Val Gly Gly Ile Glu Leu Phe His Gly Thr Tyr Lys Asp Leu Leu Phe
                165                 170                 175

AAG ACT ATA AAA CTC CCA TCT CCT TAC CTG TAC TGC AAG GAA AAG TAC         576
Lys Thr Ile Lys Leu Pro Ser Pro Tyr Leu Tyr Cys Lys Glu Lys Tyr
            180                 185                 190

GGG GAA CTC TGC CCT GAG TGC ACG GCA GAT TTA TTA AAA CAA CTG GAA         624
Gly Glu Leu Cys Pro Glu Cys Thr Ala Asp Leu Leu Lys Gln Leu Glu
        195                 200                 205

GAT ATC CTG AAG TCG CGG GAA GAT ATC GTT GCG GTC ATT ATG GAA GCG         672
Asp Ile Leu Lys Ser Arg Glu Asp Ile Val Ala Val Ile Met Glu Ala
    210                 215                 220

GGA ATT CAG GCA GCC GCG GGA ATG CTC CCC TTC CCT CCG GGA TTT TTG         720
Gly Ile Gln Ala Ala Ala Gly Met Leu Pro Phe Pro Pro Gly Phe Leu
225                 230                 235                 240
```

FIG. 3A

```
AAA GGC GTA AGG GAG CTT ACG AAG AAA TAC GAC ACT TTA ATG ATA GTT          768
Lys Gly Val Arg Glu Leu Thr Lys Lys Tyr Asp Thr Leu Met Ile Val
                245                 250                 255

GAC GAG GTT GCC ACG GGA TTT GGC AGG ACG GGA ACG ATG TTT TAC TGT          816
Asp Glu Val Ala Thr Gly Phe Gly Arg Thr Gly Thr Met Phe Tyr Cys
            260                 265                 270

GAG CAG GAA GGA GTC AGT CCG GAC TTT ATG TGT CTA GGT AAG GGT ATA          864
Glu Gln Glu Gly Val Ser Pro Asp Phe Met Cys Leu Gly Lys Gly Ile
        275                 280                 285

ACC GGA GGG TAC CTC CCG CTT GCT GCG ACA CTC ACA ACG GAC GAG GTG          912
Thr Gly Gly Tyr Leu Pro Leu Ala Ala Thr Leu Thr Thr Asp Glu Val
    290                 295                 300

TTC AAT GCC TTT TTA GGT GAG TTC GGG GAG GCA AAG CAC TTT TAC CAC          960
Phe Asn Ala Phe Leu Gly Glu Phe Gly Glu Ala Lys His Phe Tyr His
305                 310                 315                 320

GGG CAC ACC TAC ACT GGA AAT AAC CTC GCC TGT TCC GTT GCA CTC GCA         1008
Gly His Thr Tyr Thr Gly Asn Asn Leu Ala Cys Ser Val Ala Leu Ala
                325                 330                 335

AAC TTA GAA GTT TTT GAG GAA GAA AGA ACT TTA GAG AAG CTC CAA CCA         1056
Asn Leu Glu Val Phe Glu Glu Glu Arg Thr Leu Glu Lys Leu Gln Pro
            340                 345                 350

AAG ATA AAG CTT TTA AAG GAA AGG CTT CAG GAG TTC TGG GAA CTC AAG         1104
Lys Ile Lys Leu Leu Lys Glu Arg Leu Gln Glu Phe Trp Glu Leu Lys
        355                 360                 365

CAC GTT GGA GAT GTT AGA CAG CTA GGT TTT ATG GCT GGA ATA GAG CTG         1152
His Val Gly Asp Val Arg Gln Leu Gly Phe Met Ala Gly Ile Glu Leu
    370                 375                 380

GTG AAG GAC AAA GAA AAG GGA GAA CCT TTC CCT TAC GGT GAA AGG ACG         1200
Val Lys Asp Lys Glu Lys Gly Glu Pro Phe Pro Tyr Gly Glu Arg Thr
385                 390                 395                 400

GGA TTT AAG GTG GCT TAC AAG TGC AGG GAA AAA GGG GTG TTT TTG AGA         1245
Gly Phe Lys Val Ala Tyr Lys Cys Arg Glu Lys Gly Val Phe Leu Arg
                405                 410                 415

CCG CTC GGA GAC GTT ATG GTA TTG ATG ATG CCT CTT GTA ATA GAG GAA         1293
Pro Leu Gly Asp Val Met Val Leu Met Met Pro Leu Val Ile Glu Glu
            420                 425                 430

GAC GAA ATG AAC TAC GTT ATT GAT ACA CTT AAA TGG GCA ATT AAA GAG         1341
Asp Glu Met Asn Tyr Val Ile Asp Thr Leu Lys Trp Ala Ile Lys Glu
        435                 440                 445

CTT GAA AAA GAG GTG TAG                                                1359
Leu Glu Lys Glu Val End
    450
```

FIG. 3B

```
ATG ACA TAC TTA ATG AAC AAT TAC GCA AGG TTG CCC GTA AAG TTT GTA          48
Met Thr Tyr Leu Met Asn Asn Tyr Ala Arg Leu Pro Val Lys Phe Val
                5                  10                  15

AGG GGA AAA GGT GTT TAC CTG TAC GAT GAG GAA GGA AAG GAG TAT CTT          96
Arg Gly Lys Gly Val Tyr Leu Tyr Asp Glu Glu Gly Lys Glu Tyr Leu
            20                  25                  30

GAC TTT GTC TCC GGT ATA GGC GTC AAC TCC CTC GGT CAC GCT TAC CCA         144
Asp Phe Val Ser Gly Ile Gly Val Asn Ser Leu Gly His Ala Tyr Pro
        35                  40                  45

AAA CTC ACA GAA GCT CTA AAA GAA CAG GTT GAG AAA CTC CTC CAC GTT         192
Lys Leu Thr Glu Ala Leu Lys Glu Gln Val Glu Lys Leu Leu His Val
    50                  55                  60

TCA AAT CTT TAC GAA AAC CCG TGG CAG GAA GAA CTG GCT CAC AAA CTT         240
Ser Asn Leu Tyr Glu Asn Pro Trp Gln Glu Glu Leu Ala His Lys Leu
65                  70                  75                  80

GTA AAA CAC TTC TGG ACA GAA GGG AAG GTA TTT TTC GCA AAC AGC GGA         288
Val Lys His Phe Trp Thr Glu Gly Lys Val Phe Phe Ala Asn Ser Gly
                85                  90                  95

ACG GAA AGT GTA GAG GCG GCT ATA AAG CTC GCA AGG AAG TAC TGG AGG         336
Thr Glu Ser Val Glu Ala Ala Ile Lys Leu Ala Arg Lys Tyr Trp Arg
            100                 105                 110

GAT AAA GGA AAG AAC AAG TGG AAG TTT ATA TCC TTT GAA AAC TCT TTC         384
Asp Lys Gly Lys Asn Lys Trp Lys Phe Ile Ser Phe Glu Asn Ser Phe
        115                 120                 125

CAC GGG AGA ACC TAC GGT AGC CTC TCC GCA ACG GGA CAG CCA AAG TTC         432
His Gly Arg Thr Tyr Gly Ser Leu Ser Ala Thr Gly Gln Pro Lys Phe
    130                 135                 140

CAC AAA GGC TTT GAA CCT CTA GTT CCT GGA TTT TCT TAC GCA AAG CTG         480
His Lys Gly Phe Glu Pro Leu Val Pro Gly Phe Ser Tyr Ala Lys Leu
145                 150                 155                 160

AAC GAT ATA GAC AGC GTT TAC AAA CTC CTA GAC GAG GAA ACC GCG GGG         528
Asn Asp Ile Asp Ser Val Tyr Lys Leu Leu Asp Glu Glu Thr Ala Gly
                165                 170                 175

ATA ATT ATT GAA GTT ATA CAA GGA GAG GGC GGA GTA AAC GAG GCG AGT         576
Ile Ile Ile Glu Val Ile Gln Gly Glu Gly Gly Val Asn Glu Ala Ser
            180                 185                 190

GAG GAT TTT CTA AGT AAA CTC CAG GAA ATT TGT AAA GAA AAA GAT GTG         624
Glu Asp Phe Leu Ser Lys Leu Gln Glu Ile Cys Lys Glu Lys Asp Val
        195                 200                 205

CTC TTA ATT ATA GAC GAA GTG CAA ACG GGA ATA GGA AGG ACC GGG GAA         672
Leu Leu Ile Ile Asp Glu Val Gln Thr Gly Ile Gly Arg Thr Gly Glu
    210                 215                 220

TTC TAC GCA TAT CAA CAC TTC AAT CTA AAA CCG GAC GTA ATT GCG CTT         720
Phe Tyr Ala Tyr Gln His Phe Asn Leu Lys Pro Asp Val Ile Ala Leu
225                 230                 235                 240
```

FIG. 4A

```
GCG AAG GGA CTC GGA GGA GGT GTG CCA ATA GGT GCC ATC CTT GCA AGG          768
Ala Lys Gly Leu Gly Gly Gly Val Pro Ile Gly Ala Ile Leu Ala Arg
                245                 250                 255

GAA GAA GTG GCC CAG AGC TTT ACT CCC GGC TCC CAC GGC TCT ACC TTC          816
Glu Glu Val Ala Gln Ser Phe Thr Pro Gly Ser His Gly Ser Thr Phe
            260                 265                 270

GGA GGA AAC CCC TTA GCC TGC AGG GCG GGA ACA GTG GTA GTA GAT GAA          864
Gly Gly Asn Pro Leu Ala Cys Arg Ala Gly Thr Val Val Val Asp Glu
        275                 280                 285

GTT GAA AAA CTC CTG CCT CAC GTA AGG GAA GTG GGG AAT TAC TTC AAA          912
Val Glu Lys Leu Leu Pro His Val Arg Glu Val Gly Asn Tyr Phe Lys
    290                 295                 300

GAA AAA CTG AAG GAA CTC GGC AAA GGA AAG GTA AAG GGA AGA GGA TTG          960
Glu Lys Leu Lys Glu Leu Gly Lys Gly Lys Val Lys Gly Arg Gly Leu
305                 310                 315                 320

ATG CTC GGT CTT GAA CTT GAA AGA GAG TGT AAA GAT TAC GTT CTC AAG         1008
Met Leu Gly Leu Glu Leu Glu Arg Glu Cys Lys Asp Tyr Val Leu Lys
                325                 330                 335

GCT CTT GAA AGG GAC TTC TCA TAA                                         1032
Ala Leu Glu Arg Asp Phe Ser End
            340
```

FIG. 4B

```
ATG CGG AAA CTG GCC GAG CGG GCG CAG AAA CTG AGC CCC TCT CCC ACC          48
Met Arg Lys Leu Ala Glu Arg Ala Gln Lys Leu Ser Pro Ser Pro Thr
                5                   10                  15

CTC TCG GTG GAC ACC AAG GCC AAG GAG CTT TTG CGG CAG GGG GAA AGG          96
Leu Ser Val Asp Thr Lys Ala Lys Glu Leu Leu Arg Gln Gly Glu Arg
            20                  25                  30

GTC ATC AAT TTC GGG GCG GGG GAG CCG GAC TTC GAT ACA CCG GAA CAC         144
Val Ile Asn Phe Gly Ala Gly Glu Pro Asp Phe Asp Thr Pro Glu His
        35                  40                  45

ATC AAG GAA GCG GCG AAG CGA GCT TTA GAT CAG GGC TTC ACC AAG TAC         192
Ile Lys Glu Ala Ala Lys Arg Ala Leu Asp Gln Gly Phe Thr Lys Tyr
    50                  55                  60

ACG CCG GTG GCT GGG ATC TTA CCT CTT CGG GAG GCC ATA TGC GAG AAG         240
Thr Pro Val Ala Gly Ile Leu Pro Leu Arg Glu Ala Ile Cys Glu Lys
65                  70                  75                  80

CTT TAC CGC GAC AAT CAA CTG GAA TAC AGC CCG AAT GAG ATC GTG GTC         288
Leu Tyr Arg Asp Asn Gln Leu Glu Tyr Ser Pro Asn Glu Ile Val Val
                85                  90                  95

TCC TGT GGC GCC AAG CAT TCT ATT TTC AAC GCT CTG CAG GTC CTC CTG         336
Ser Cys Gly Ala Lys His Ser Ile Phe Asn Ala Leu Gln Val Leu Leu
            100                 105                 110

GAC CCG GGG GAC GAG GTG ATA ATC CCC GTC CCC TAC TGG ACT TCC TAT         384
Asp Pro Gly Asp Glu Val Ile Ile Pro Val Pro Tyr Trp Thr Ser Tyr
        115                 120                 125

CCG GAG CAG GTG AAG CTG GCG GGA GGG GTG CCG GTT TTC GTC CCC ACC         432
Pro Glu Gln Val Lys Leu Ala Gly Gly Val Pro Val Phe Val Pro Thr
    130                 135                 140

TCT CCC GAG AAC GAC TTC AAG CTC AGG CCG GAA GAT CTA CGT GCG GCT         480
Ser Pro Glu Asn Asp Phe Lys Leu Arg Pro Glu Asp Leu Arg Ala Ala
145                 150                 155                 160

GTA ACC CCG CGC ACC CGC CTT TTG ATC CTC AAT TCC CCG GCC AAC CCC         528
Val Thr Pro Arg Thr Arg Leu Leu Ile Leu Asn Ser Pro Ala Asn Pro
                165                 170                 175

ACA GGC ACC GTT TAC CGC CGG GAG GAA CTT ATC GGC TTA GCG GAG GTA         576
Thr Gly Thr Val Tyr Arg Arg Glu Glu Leu Ile Gly Leu Ala Glu Val
            180                 185                 190

GCC CTG GAG GCC GAC CTA TGG ATC TTG TCG GAC GAG ATC TAC GAA AAG         624
Ala Leu Glu Ala Asp Leu Trp Ile Leu Ser Asp Glu Ile Tyr Glu Lys
        195                 200                 205

CTG ATC TAC GAC GGG ATG GAG CAC GTG AGC ATA GCC GCG CTC GAC CCG         672
Leu Ile Tyr Asp Gly Met Glu His Val Ser Ile Ala Ala Leu Asp Pro
    210                 215                 220

GAG GTC AAA AAG CGC ACG ATT GTG GTA AAC GGT GTT TCC AAG GCT TAC         720
Glu Val Lys Lys Arg Thr Ile Val Val Asn Gly Val Ser Lys Ala Tyr
225                 230                 235                 240
```

FIG. 5A

```
GCC ATG ACC GGT TGG CGC ATA GGT TAT GCT GCC GCT CCC CGG CCG ATA          768
Ala Met Thr Gly Trp Arg Ile Gly Tyr Ala Ala Ala Pro Arg Pro Ile
                245                 250                 255

GCC CAG GCC ATG ACC AAC CTC CAA AGC CAC AGT ACC TCT AAC CCC ACT          816
Ala Gln Ala Met Thr Asn Leu Gln Ser His Ser Thr Ser Asn Pro Thr
            260                 265                 270

TCC GTA GCC CAG GCG GCG GCG CTG GCC GCT CTG AAG GGG CCA CAA GAG          864
Ser Val Ala Gln Ala Ala Ala Leu Ala Ala Leu Lys Gly Pro Gln Glu
        275                 280                 285

CCG GTG GAG AAC ATG CGC CGG GCT TTT CAA AAG CGG CGG GAT TTC ATC          912
Pro Val Glu Asn Met Arg Arg Ala Phe Gln Lys Arg Arg Asp Phe Ile
    290                 295                 300

TGG CAG TAC CTA AAC TCC TTA CCC GGA GTG CGC TGC CCC AAA CCT TTA          960
Trp Gln Tyr Leu Asn Ser Leu Pro Gly Val Arg Cys Pro Lys Pro Leu
305                 310                 315                 320

GGG GCC TTT TAC GTC TTT CCA GAA GTT GAG CGG GCT TTT GGG CCG CCG         1008
Gly Ala Phe Tyr Val Phe Pro Glu Val Glu Arg Ala Phe Gly Pro Pro
                325                 330                 335

TCT AAA AGG ACG GGA AAT ACT ACC GCT AGC GAC CTG GCC CTT TTC CTC         1056
Ser Lys Arg Thr Gly Asn Thr Thr Ala Ser Asp Leu Ala Leu Phe Leu
            340                 345                 350

CTG GAA GAG ATA AAA GTG GCC ACC GTG GCT GGG GCT GCC TTT GGG GAC         1104
Leu Glu Glu Ile Lys Val Ala Thr Val Ala Gly Ala Ala Phe Gly Asp
        355                 360                 365

GAT CGC TAC CTG CGC TTT TCC TAC GCC CTG CGG CTG GAA GAT ATC GAA         1152
Asp Arg Tyr Leu Arg Phe Ser Tyr Ala Leu Arg Leu Glu Asp Ile Glu
    370                 375                 380

GAG GGG ATG CAA CGG TTT AAA GAA TTG ATC GAA GCG GCA CTT TAA             1197
Glu Gly Met Gln Arg Phe Lys Glu Leu Ile Glu Ala Ala Leu End
385                 390                 395
```

FIG. 5B

```
ATG TGC GGG ATA GTC GGA TAC GTA GGG AGG GAT TTA GCC CTT CCT ATA          48
Met Cys Gly Ile Val Gly Tyr Val Gly Arg Asp Leu Ala Leu Pro Ile
                5                  10                  15

GTC CTC GGA GCT CTT GAG AGA CTC GAA TAC AGG GGT TAC GAC TCC GCG          96
Val Leu Gly Ala Leu Glu Arg Leu Glu Tyr Arg Gly Tyr Asp Ser Ala
            20                  25                  30

GGA GTT GCC CTT ATA GAA GAC GGG AAA CTC ATA GTT GAA AAG AAG AAG         144
Gly Val Ala Leu Ile Glu Asp Gly Lys Leu Ile Val Glu Lys Lys Lys
        35                  40                  45

GGA AAG ATA AGG GAA CTC GTT AAA GCG CTA TGG GGA AAG GAT TAC AAG         192
Gly Lys Ile Arg Glu Leu Val Lys Ala Leu Trp Gly Lys Asp Tyr Lys
    50                  55                  60

GCT AAA ACG GGT ATA GGT CAC ACA CGC TGG GCA ACC CAC GGA AAG CCC         240
Ala Lys Thr Gly Ile Gly His Thr Arg Trp Ala Thr His Gly Lys Pro
65                  70                  75                  80

ACG GAC GAG AAC GCC CAC CCC CAC ACC GAC GAA AAA GGT GAG TTT GCA         288
Thr Asp Glu Asn Ala His Pro His Thr Asp Glu Lys Gly Glu Phe Ala
                85                  90                  95

GTA GTT CAC AAC GGG ATA ATA GAA AAC TAC TTA GAA CTA AAA GAG GAA         336
Val Val His Asn Gly Ile Ile Glu Asn Tyr Leu Glu Leu Lys Glu Glu
            100                 105                 110

CTA AAG AAG GAA GGT GTA AAG TTC AGG TCC GAA ACA GAC ACA GAA GTT         384
Leu Lys Lys Glu Gly Val Lys Phe Arg Ser Glu Thr Asp Thr Glu Val
        115                 120                 125

ATA GCC CAC CTC ATA GCG AAG AAC TAC AGG GGG GAC TTA CTG GAG GCC         432
Ile Ala His Leu Ile Ala Lys Asn Tyr Arg Gly Asp Leu Leu Glu Ala
    130                 135                 140

GTT TTA AAA ACC GTA AAG AAA TTA AAG GGT GCT TTT GCC TTT GCG GTT         480
Val Leu Lys Thr Val Lys Lys Leu Lys Gly Ala Phe Ala Phe Ala Val
145                 150                 155                 160

ATA ACG GTT CAC GAA CCA AAC AGA CTA ATA GGA GTG AAG CAG GGG AGT         528
Ile Thr Val His Glu Pro Asn Arg Leu Ile Gly Val Lys Gln Gly Ser
                165                 170                 175

CCT TTA ATC GTC GGA CTC GGA GAA GGA GAA AAC TTC CTC GCT TCA GAT         576
Pro Leu Ile Val Gly Leu Gly Glu Gly Glu Asn Phe Leu Ala Ser Asp
            180                 185                 190

ATT CCC GCA ATA CTT CCT TAC ACG AAA AAG ATT ATT GTT CTT GAT GAC         624
Ile Pro Ala Ile Leu Pro Tyr Thr Lys Lys Ile Ile Val Leu Asp Asp
        195                 200                 205

GGG GAA ATA GCG GAC CTG ACT CCC GAC ACT GTG AAC ATT TAC AAC TTT         672
Gly Glu Ile Ala Asp Leu Thr Pro Asp Thr Val Asn Ile Tyr Asn Phe
    210                 215                 220

GAG GGA GAG CCC GTT TCA AAG GAA GTA ATG ATT ACG CCC TGG GAT CTT         720
Glu Gly Glu Pro Val Ser Lys Glu Val Met Ile Thr Pro Trp Asp Leu
225                 230                 235                 240
```

FIG. 6A

```
GTT TCT GCG GAA AAG GGT GGT TTT AAA CAC TTC ATG CTA AAA GAG ATA          768
Val Ser Ala Glu Lys Gly Gly Phe Lys His Phe Met Leu Lys Glu Ile
                245                 250                 255

TAC GAA CAG CCC AAA GCC ATA AAC GAC ACA CTC AAG GGT TTC CTC TCA          816
Tyr Glu Gln Pro Lys Ala Ile Asn Asp Thr Leu Lys Gly Phe Leu Ser
            260                 265                 270

ACC GAA GAC GCA ATA CCC TTT AAG TTA AAA GAC TTC AGA AGG GTT TTA          864
Thr Glu Asp Ala Ile Pro Phe Lys Leu Lys Asp Phe Arg Arg Val Leu
        275                 280                 285

ATA ATA GCG TGC GGG ACC TCT TAC CAC GCG GGC TTC GTC GGA AAG TAC          912
Ile Ile Ala Cys Gly Thr Ser Tyr His Ala Gly Phe Val Gly Lys Tyr
    290                 295                 300

TGG ATA GAG AGA TTT GCA GGT GTT CCC ACA GAG GTA ATT TAC GCT TCG          960
Trp Ile Glu Arg Phe Ala Gly Val Pro Thr Glu Val Ile Tyr Ala Ser
305                 310                 315                 320

GAA TTC AGG TAT GCG GAC GTT CCC GTT TCG GAC AAG GAT ATC GTT ATC         1008
Glu Phe Arg Tyr Ala Asp Val Pro Val Ser Asp Lys Asp Ile Val Ile
                325                 330                 335

GGA ATT TCC CAG TCA GGA GAG ACC GCT GAC ACA AAG TTT GCC CTT CAG         1056
Gly Ile Ser Gln Ser Gly Glu Thr Ala Asp Thr Lys Phe Ala Leu Gln
            340                 345                 350

TCC GCA AAG GAA AAG GGA GCC TTT ACC GTG GGA CTC GTA AAC GTA GTG         1104
Ser Ala Lys Glu Lys Gly Ala Phe Thr Val Gly Leu Val Asn Val Val
        355                 360                 365

GGA AGT GCC ATA GAC AGG GAG TCG GAC TTT TCC CTT CAC ACA CAT GCG         1152
Gly Ser Ala Ile Asp Arg Glu Ser Asp Phe Ser Leu His Thr His Ala
    370                 375                 380

GGA CCC GAA ATA GGC GTG GCG GCT ACA AAG ACC TTC ACC GCA CAG TTC         1200
Gly Pro Glu Ile Gly Val Ala Ala Thr Lys Thr Phe Thr Ala Gln Phe
385                 390                 395                 400

ACC GCA CTC TAC GCC CTT TCG GTA AGG GAA AGT GAG GAG AGG GAA AAT         1248
Thr Ala Leu Tyr Ala Leu Ser Val Arg Glu Ser Glu Glu Arg Glu Asn
                405                 410                 415

CTA ATA AGA CTC CTT GAA AAG GTT CCA TCA CTC GTT GAA CAA ACA CTG         1296
Leu Ile Arg Leu Leu Glu Lys Val Pro Ser Leu Val Glu Gln Thr Leu
            420                 425                 430

AAC ACC GCA GAA GAA GTG GAG AAG GTA GCG GAA AAG TAC ATG AAA AAG         1344
Asn Thr Ala Glu Glu Val Glu Lys Val Ala Glu Lys Tyr Met Lys Lys
        435                 440                 445

AAA AAC ATG CTT TAC CTC GGA AGG TAC TTA AAT TAC CCC ATA GCG CTG         1392
Lys Asn Met Leu Tyr Leu Gly Arg Tyr Leu Asn Tyr Pro Ile Ala Leu
    450                 455                 460

GAG GGA GCT CTT AAA CTT AAA GAA ATT TCT TAC ATA CAC GCG GAA GGT         1440
Glu Gly Ala Leu Lys Leu Lys Glu Ile Ser Tyr Ile His Ala Glu Gly
465                 470                 475                 480

TAT CCC GCA GGG GAG ATG AAG CAC GGT CCC ATA GCC CTC ATA GAC GAA         1488
Tyr Pro Ala Gly Glu Met Lys His Gly Pro Ile Ala Leu Ile Asp Glu
                485                 490                 495
```

FIG. 6B

```
AAC ATG CCG GTT GTG GTA ATC GCA CCG AAA GAC AGG GTT TAC GAG AAG          1536
Asn Met Pro Val Val Val Ile Ala Pro Lys Asp Arg Val Tyr Glu Lys
            500                 505                 510

ATA CTC TCA AAC GTA GAA GAG GTT CTC GCA AGA AAG GGA AGG GTT ATT          1584
Ile Leu Ser Asn Val Glu Glu Val Leu Ala Arg Lys Gly Arg Val Ile
        515                 520                 525

TCT GTA GGC TTT AAA GGA GAC GAA ACT CTC AAA AGC AAA TCC GAG AGC          1632
Ser Val Gly Phe Lys Gly Asp Glu Thr Leu Lys Ser Lys Ser Glu Ser
    530                 535                 540

GTT ATG GAA ATC CCG AAG GCA GAA GAA CCG ATA ACT CCT TTC TTG ACG          1680
Val Met Glu Ile Pro Lys Ala Glu Glu Pro Ile Thr Pro Phe Leu Thr
545                 550                 555                 560

GTA ATA CCC CTG CAA CTC TTT GCC TAC TTT ATA GCG AGC AAA CTG GGA          1728
Val Ile Pro Leu Gln Leu Phe Ala Tyr Phe Ile Ala Ser Lys Leu Gly
                565                 570                 575
580

CTG GAT GTG GAT CAG CCG AGA AAT CTC GCC AAA ACG GTC ACG GTG GAA          1776
Leu Asp Val Asp Gln Pro Arg Asn Leu Ala Lys Thr Val Thr Val Glu
            580                 585                 590

TAA                                                                      1779
End
```

FIG. 6C

```
ATG ATA CCC CAG AGG ATT AAG GAA CTT GAA GCT TAC AAG ACG GAG GTC          48
Met Ile Pro Gln Arg Ile Lys Glu Leu Glu Ala Tyr Lys Thr Glu Val
                5                  10                  15

ACT CCC GCC TCC GTC AGG CTT TCC TCT AAC GAA TTC CCC TAC GAC TTT          96
Thr Pro Ala Ser Val Arg Leu Ser Ser Asn Glu Phe Pro Tyr Asp Phe
            20                  25                  30

CCC GAG GAG ATA AAA CAA AGG GCC TTA GAA GAA TTA AAA AAG GTT CCC         144
Pro Glu Glu Ile Lys Gln Arg Ala Leu Glu Glu Leu Lys Lys Val Pro
        35                  40                  45

TTG AAC AAA TAC CCA GAC CCC GAA GCG AAA GAG TTA AAA GCG GTT CTT         192
Leu Asn Lys Tyr Pro Asp Pro Glu Ala Lys Glu Leu Lys Ala Val Leu
    50                  55                  60

GCG GAT TTT TTC GGC GTT AAG GAA GAA AAT TTA GTT CTC GGT AAC GGT         240
Ala Asp Phe Phe Gly Val Lys Glu Glu Asn Leu Val Leu Gly Asn Gly
65                  70                  75                  80

TCG GAC GAA CTC ATA TAC TAC CTC TCA ATA GCT ATA GGT GAA CTT TAC         288
Ser Asp Glu Leu Ile Tyr Tyr Leu Ser Ile Ala Ile Gly Glu Leu Tyr
                85                  90                  95

ATA CCC GTT TAC ATA CCT GTT CCC ACC TTT CCC ATG TAC GAG ATA AGT         336
Ile Pro Val Tyr Ile Pro Val Pro Thr Phe Pro Met Tyr Glu Ile Ser
            100                 105                 110

GCG AAA GTT CTC GGA AGA CCC CTC GTA AAG GTT CAA CTG GAC GAA AAC         384
Ala Lys Val Leu Gly Arg Pro Leu Val Lys Val Gln Leu Asp Glu Asn
        115                 120                 125

TTT GAT ATA GAC TTA GAA AGA AGT ATT GAA TTA ATA GAG AAA GAA AAA         432
Phe Asp Ile Asp Leu Glu Arg Ser Ile Glu Leu Ile Glu Lys Glu Lys
    130                 135                 140

CCC GTT CTC GGG TAC TTT GCT TAC CCA AAC AAC CCC ACG GGA AAC CTC         480
Pro Val Leu Gly Tyr Phe Ala Tyr Pro Asn Asn Pro Thr Gly Asn Leu
145                 150                 155                 160

TTT TCC AGG GGA AAG ATT GAG GAG ATA AGA AAC AGG GGT GTT TTC TGT         528
Phe Ser Arg Gly Lys Ile Glu Glu Ile Arg Asn Arg Gly Val Phe Cys
                165                 170                 175

GTA ATA GAC GAA GCC TAC TAT CAT TAC TCC GGA GAA ACC TTT CTG GAA         576
Val Ile Asp Glu Ala Tyr Tyr His Tyr Ser Gly Glu Thr Phe Leu Glu
            180                 185                 190

GAC GCG CTC AAA AGG GAA GAT ACG GTA GTT TTG AGG ACA CTT TCA AAA         624
Asp Ala Leu Lys Arg Glu Asp Thr Val Val Leu Arg Thr Leu Ser Lys
        195                 200                 205

ATC GGT ATG GCG AGT TTA AGG GTA GGG ATT TTA ATA GGG AAG GGG GAA         672
Ile Gly Met Ala Ser Leu Arg Val Gly Ile Leu Ile Gly Lys Gly Glu
    210                 215                 220

ATC GTC TCA GAA ATT AAC AAG GTG AGA CTC CCC TTC AAC GTG ACC TAC         720
Ile Val Ser Glu Ile Asn Lys Val Arg Leu Pro Phe Asn Val Thr Tyr
225                 230                 235                 240
```

FIG. 7A

```
CCC TCT CAG GTG ATG GCA AAA GTT CTC CTC ACG GAG GGA AGA GAA TTC          768
Pro Ser Gln Val Met Ala Lys Val Leu Leu Thr Glu Gly Arg Glu Phe
                245                 250                 255

CTA ATG GAA AAG ATA CAG GAG GTT GTA ACA GAG CGA GAA AGG ATG TAC          816
Leu Met Glu Lys Ile Gln Glu Val Val Thr Glu Arg Glu Arg Met Tyr
            260                 265                 270

GAC GAA ATG AAG AAA ATA GAA GGA GTT GAG GTT TTT CCG AGT AAG GCT          864
Asp Glu Met Lys Lys Ile Glu Gly Val Glu Val Phe Pro Ser Lys Ala
        275                 280                 285

AAC TTC TTG CTT TTC AGA ACG CCT TAC CCC GCC CAC GAG GTT TAT CAG          912
Asn Phe Leu Leu Phe Arg Thr Pro Tyr Pro Ala His Glu Val Tyr Gln
    290                 295                 300

GAG CTA CTG AAA AGG GAT GTC CTC GTC AGG AAC GTA TCT TAC ATG GAA          960
Glu Leu Leu Lys Arg Asp Val Leu Val Arg Asn Val Ser Tyr Met Glu
305                 310                 315                 320

GGA CTC CAA AAG TGC CTC AGG GTA AGC GTA GGG AAA CCG GAA GAA AAC         1008
Gly Leu Gln Lys Cys Leu Arg Val Ser Val Gly Lys Pro Glu Glu Asn
                325                 330                 335

AAC AAG TTT CTG GAA GCA CTG GAG GAG AGT ATA AAA TCC CTT TCA AGC         1056
Asn Lys Phe Leu Glu Ala Leu Glu Glu Ser Ile Lys Ser Leu Ser Ser
            340                 345                 350

TCT CTT TAA                                                             1065
Ser Leu End
```

FIG. 7B

```
ATG AAG CCG TAC GCT AAA TAT ATC TGG CTT GAC GGC AGA ATA CTT AAG          48
Met Lys Pro Tyr Ala Lys Tyr Ile Trp Leu Asp Gly Arg Ile Leu Lys
                5                  10                  15

TGG GAA GAC GCG AAA ATA CAC GTG TTG ACT CAC GCG CTT CAC TAC GGA          96
Trp Glu Asp Ala Lys Ile His Val Leu Thr His Ala Leu His Tyr Gly
            20                  25                  30

ACC TCT ATA TTC GAG GGA ATA AGA GGG TAT TGG AAC GGC GAT AAT TTG         144
Thr Ser Ile Phe Glu Gly Ile Arg Gly Tyr Trp Asn Gly Asp Asn Leu
        35                  40                  45

CTC GTC TTT AGG TTA GAA GAA CAC ATC GAC CGC ATG TAC AGA TCG GCT         192
Leu Val Phe Arg Leu Glu Glu His Ile Asp Arg Met Tyr Arg Ser Ala
    50                  55                  60

AAG ATA CTA GGC ATA AAT ATT CCG TAT ACA AGA GAG GAA GTC CGC CAA         240
Lys Ile Leu Gly Ile Asn Ile Pro Tyr Thr Arg Glu Glu Val Arg Gln
65                  70                  75                  80

GCT GTA CTA GAG ACC ATA AAG GCT AAT AAC TTC CGA GAG GAT GTC TAC         288
Ala Val Leu Glu Thr Ile Lys Ala Asn Asn Phe Arg Glu Asp Val Tyr
                85                  90                  95

ATA AGA CCT GTG GCG TTT GTC GCC TCG CAG ACG GTG ACG CTT GAC ATA         336
Ile Arg Pro Val Ala Phe Val Ala Ser Gln Thr Val Thr Leu Asp Ile
            100                 105                 110

AGA AAT TTG GAA GTC TCC CTC GCG GTT ATT GTA TTC CCA TTT GGC AAA         384
Arg Asn Leu Glu Val Ser Leu Ala Val Ile Val Phe Pro Phe Gly Lys
        115                 120                 125

TAC CTC TCG CCC AAC GGC ATT AAG GCA ACG ATT GTA AGC TGG CGT AGA         432
Tyr Leu Ser Pro Asn Gly Ile Lys Ala Thr Ile Val Ser Trp Arg Arg
    130                 135                 140

GTA CAT AAT ACA ATG CTC CCT GTG ATG GCA AAA ATC GGC GGT ATA TAT         480
Val His Asn Thr Met Leu Pro Val Met Ala Lys Ile Gly Gly Ile Tyr
145                 150                 155                 160

GTA AAC TCT GTA CTT GCG CTT GTA GAG GCT AGA AGC AGG GGA TTT GAC         528
Val Asn Ser Val Leu Ala Leu Val Glu Ala Arg Ser Arg Gly Phe Asp
                165                 170                 175

GAG GCT TTA TTA ATG GAC GTT AAC GGT TAT GTT GTT GAG GGT TCT GGA         576
Glu Ala Leu Leu Met Asp Val Asn Gly Tyr Val Val Glu Gly Ser Gly
            180                 185                 190

GAG AAT ATT TTC ATT GTC AGA GGT GGA AGG CTT TTC ACG CCG CCA GTA         624
Glu Asn Ile Phe Ile Val Arg Gly Gly Arg Leu Phe Thr Pro Pro Val
        195                 200                 205

CAC GAA TCT ATC CTC GAG GGA ATT ACG AGG GAT ACG GTA ATA AAG CTC         672
His Glu Ser Ile Leu Glu Gly Ile Thr Arg Asp Thr Val Ile Lys Leu
    210                 215                 220

AGC GGG GAT GTG GGA CTT CGG GTG GAG GAA AAG CCT ATT ACG AGG GAG         720
Ser Gly Asp Val Gly Leu Arg Val Glu Glu Lys Pro Ile Thr Arg Glu
225                 230                 235                 240
```

FIG. 8A

```
GAG GTG TAT ACA GCC GAC GAG GTG TTT TTA GTA GGA ACC GCC GCA GAG          768
Glu Val Tyr Thr Ala Asp Glu Val Phe Leu Val Gly Thr Ala Ala Glu
                245                 250                 255

ATA ACG CCA GTG GTG GAG GTT GAC GGC AGA ACA ATC GGC ACA GGC AAG          816
Ile Thr Pro Val Val Glu Val Asp Gly Arg Thr Ile Gly Thr Gly Lys
            260                 265                 270

CCG GGC CCC ATT ACG ACA AAA ATA GCT GAG CTG TAC TCA AAC GTC GTG          864
Pro Gly Pro Ile Thr Thr Lys Ile Ala Glu Leu Tyr Ser Asn Val Val
        275                 280                 285

AGA GGC AAA GTA GAG AAA TAC TTA AAT TGG ATC ACT CCT GTG TAT TAG          912

Arg Gly Lys Val Glu Lys Tyr Leu Asn Trp Ile Thr Pro Val Tyr End
    290                 295                 300
```

FIG. 8B

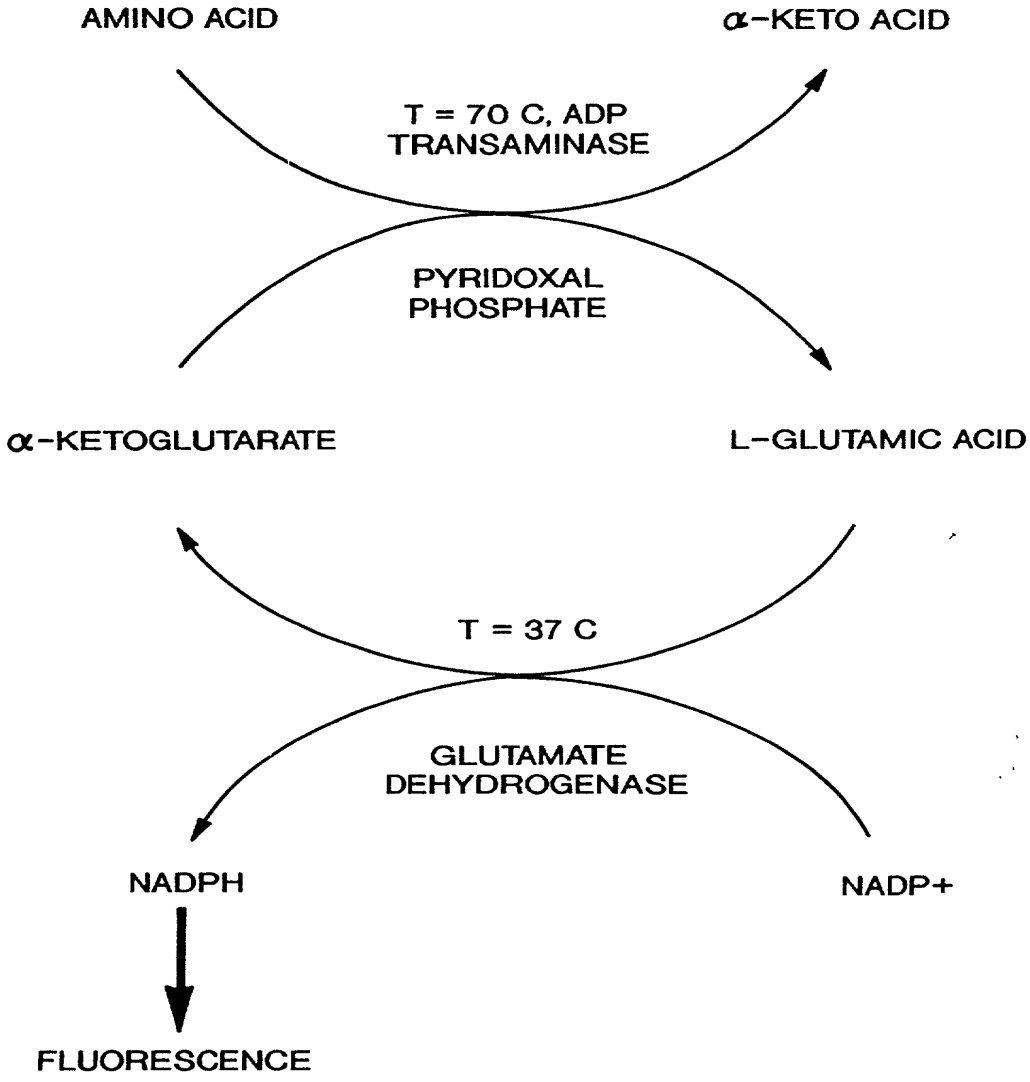
AMINO ACID
α-KETO ACID
T = 70 C, ADP
TRANSAMINASE
PYRIDOXAL
PHOSPHATE
α-KETOGLUTARATE
L-GLUTAMIC ACID
T = 37 C
GLUTAMATE
DEHYDROGENASE
NADPH
NADP+
FLUORESCENCE

FIG. 9

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TRANSAMINASES AND AMINOTRANSFERASES

the specification of which [ ] is attached hereto or [X] was filed on February 9, 1996 as Application Serial No. 08/599,171 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s):

			Priority Claimed	
			Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	☐	☐

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	Pending (Status - patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status - patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: John N. Bain (Reg. No. 18,651); John G. Gilfillan, III (Reg. No. 22,746); Elliot M. Olstein (Reg. No. 24,025); Raymond J. Lillie (Reg. No. 31,778); Charles J. Herron (Reg. No. 28,019); William Squire (Reg. No. 25,378); Kenneth S. Weitzman (Reg No. 36,306); and Gregory Ferraro (Reg. No. 36,134). Address correspondence and telephone calls to Charles J. Herron c/o Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein, 6 Becker Farm Road, Roseland, NJ 07068 - (201) 994-1700.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of inventor: Patrick V. Warren
Inventor's signature: Patrick V. Warren Date: 5/11/96
Residence: 3507 Sheffield Avenue, Philadelphia, PA ~~19165~~ 19136 Citizenship: United States
Post Office Address: same Pww 5/11/96

Full name of inventor: Ronald V. Swanson
Inventor's signature: Ronald V. Swanson Date: 3/12/96
Residence: 309 No. Lemon Street, Apt. A, Media, PA 19063 Citizenship: United States
Post Office Address: same

SEQUENCE LISTING

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SWANSON, Ronald V.

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TRANSAMINASES AND AMINOTRANSFERASES

(iii) NUMBER OF SEQUENCES: 32

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(C) CITY: La Jolla
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 92037

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 3.5 INCH DISKETTE
(B) COMPUTER: IBM PS/2
(C) OPERATING SYSTEM: MS-DOS
(D) SOFTWARE: WORD PERFECT 5.1

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: Unassigned
(B) FILING DATE: Concurrently
(C) CLASSIFICATION: Unassigned

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 08/599,171
(B) FILING DATE: 2/9/96
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Lisa A. Haile, Ph.D.
(B) REGISTRATION NUMBER: 38,347
(C) REFERENCE/DOCKET NUMBER: 09010/016002

(ix) TELECOMMUNICATION INFORMATION:
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(B) TELEFAX: 619-678-5099

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 52 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CCGAGAATTC ATTAAAGAGG AGAAATTAAC TATGATTGAA GACCCTATGG AC 52

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 31 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

CGGAAGATCT TTAAGCACTT CTCTCAGGTT C 31

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 52 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CCGAGAATTC ATTAAAGAGG AGAAATTAAC TATGGACAGG CTTGAAAAAG TA 52

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 31 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CGGAAGATCT TCAGCTAAGC TTCTCTAAGA A 31

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 52 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CCGACAATTG ATTAAAGAGG AGAAATTAAC TATGTGGGAA TTAGACCCTA AA 52

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 31 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CGGAGGATCC CTACACCTGT TTTTCAAGCT C 31

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 52 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CCGACAATTG ATTAAAGAGG AGAAATTAAC TATGACATAC TTAATGAACA AT 52

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 31 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

CGGAAGATCT TTATGAGAAG TCCCTTTCAA G 31

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 52 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CCGAGAATTC ATTAAAGAGG AGAAATTAAC TATGCGGAAA CTGGCCGAGC GG 52

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 31 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CGGAGGATCC TTAAAGTGCC GCTTCGATCA A 31

(2) INFORMATION FOR SEQ ID NO:11:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 52 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CCGACAATTG ATTAAAGAGG AGAAATTAAC TATGTGCGGG ATAGTCGGAT AC 52

(2) INFORMATION FOR SEQ ID NO:12:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 31 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CGGAAGATCT TTATTCCACC GTGACCGTTT T 31

(2) INFORMATION FOR SEQ ID NO:13:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 52 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CCGACAATTG ATTAAAGAGG AGAAATTAAC TATGATACCC CAGAGGATTA AG 52

(2) INFORMATION FOR SEQ ID NO:14:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 31 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CGGAAGATCT TTAAAGAGAG CTTGAAAGGG A 31

(2) INFORMATION FOR SEQ ID NO:15:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 52 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CCGAGAATTC ATTAAAGAGG AGAAATTAAC TATGAAGCCG TACGCTAAAT AT 52

(2) INFORMATION FOR SEQ ID NO:16:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 31 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CGGAAGATCT CTAATACACA GGAGTGATCC A 31

(2) INFORMATION FOR SEQ ID NO:17:
(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 1245 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: GENOMIC DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
ATG ATT GAA GAC CCT ATG GAC TGG GCT TTT CCG AGG ATA AAG AGA CTG          48
Met Ile Glu Asp Pro Met Asp Trp Ala Phe Pro Arg Ile Lys Arg Leu
                5                  10                  15

CCT CAG TAT GTC TTC TCT CTC GTT AAC GAA CTC AAG TAC AAG CTA AGG          96
Pro Gln Tyr Val Phe Ser Leu Val Asn Glu Leu Lys Tyr Lys Leu Arg
            20                  25                  30

CGT GAA GGC GAA GAT GTA GTG GAT CTT GGT ATG GGC AAT CCT AAC ATG         144
Arg Glu Gly Glu Asp Val Val Asp Leu Gly Met Gly Asn Pro Asn Met
        35                  40                  45

CCT CCA GCA AAG CAC ATA ATA GAT AAA CTC TGC GAA GTG GCT CAA AAG         192
Pro Pro Ala Lys His Ile Ile Asp Lys Leu Cys Glu Val Ala Gln Lys
    50                  55                  60
```

```
CCG AAC GTT CAC GGA TAT TCT GCG TCA AGG GGC ATA CCA AGA CTG AGA          240
Pro Asn Val His Gly Tyr Ser Ala Ser Arg Gly Ile Pro Arg Leu Arg
 65                  70                  75                  80

AAG GCT ATA TGT AAC TTC TAC GAA GAA AGG TAC GGA GTG AAA CTC GAC          288
Lys Ala Ile Cys Asn Phe Tyr Glu Glu Arg Tyr Gly Val Lys Leu Asp
                85                  90                  95

CCT GAG AGG GAG GCT ATA CTA ACA ATC GGT GCA AAG GAA GGG TAT TCT          336
Pro Glu Arg Glu Ala Ile Leu Thr Ile Gly Ala Lys Glu Gly Tyr Ser
           100                 105                 110

CAT TTG ATG CTT GCG ATG ATA TCT CCG GGT GAT ACG GTA ATA GTT CCT          384
His Leu Met Leu Ala Met Ile Ser Pro Gly Asp Thr Val Ile Val Pro
       115                 120                 125

AAT CCC ACC TAT CCT ATT CAC TAT TAC GCT CCC ATA ATT GCA GGA GGG          432
Asn Pro Thr Tyr Pro Ile His Tyr Tyr Ala Pro Ile Ile Ala Gly Gly
   130                 135                 140

GAA GTT CAC TCA ATA CCC CTT AAC TTC TCG GAC GAT CAA GAT CAT CAG          480
Glu Val His Ser Ile Pro Leu Asn Phe Ser Asp Asp Gln Asp His Gln
145                 150                 155                 160

GAA GAG TTT TTA AGG AGG CTT TAC GAG ATA GTA AAA ACC GCG ATG CCA          528
Glu Glu Phe Leu Arg Arg Leu Tyr Glu Ile Val Lys Thr Ala Met Pro
                165                 170                 175

AAA CCC AAG GCT GTC GTC ATA AGC TTT CCT CAC AAT CCA ACG ACC ATA          576
Lys Pro Lys Ala Val Val Ile Ser Phe Pro His Asn Pro Thr Thr Ile
           180                 185                 190

ACG GTA GAA AAG GAC TTT TTT AAA GAA ATA GTT AAG TTT GCA AAG GAA          624
Thr Val Glu Lys Asp Phe Phe Lys Glu Ile Val Lys Phe Ala Lys Glu
       195                 200                 205

CAC GGT CTC TGG ATA ATA CAC GAT TTT GCG TAT GCG GAT ATA GCC TTT          672
His Gly Leu Trp Ile Ile His Asp Phe Ala Tyr Ala Asp Ile Ala Phe
   210                 215                 220

GAC GGT TAC AAG CCC CCC TCA ATA CTC GAA ATA GAA GGT GCT AAA GAC          720
Asp Gly Tyr Lys Pro Pro Ser Ile Leu Glu Ile Glu Gly Ala Lys Asp
225                 230                 235                 240

GTT GCG GTT GAG CTC TAC TCC ATG TCA AAG GGC TTT TCA ATG GCG GGC          768
Val Ala Val Glu Leu Tyr Ser Met Ser Lys Gly Phe Ser Met Ala Gly
                245                 250                 255

TGG AGG GTA GCC TTT GTC GTT GGA AAC GAA ATA CTC ATA AAA AAC CTT          816
Trp Arg Val Ala Phe Val Val Gly Asn Glu Ile Leu Ile Lys Asn Leu
           260                 265                 270

GCA CAC CTC AAA AGC TAC TTG GAT TAC GGT ATA TTT ACT CCC ATA CAG          864
Ala His Leu Lys Ser Tyr Leu Asp Tyr Gly Ile Phe Thr Pro Ile Gln
       275                 280                 285

GTG GCC TCT ATT ATC GCA TTA GAG AGC CCC TAC GAA ATC GTG GAA AAA          912
Val Ala Ser Ile Ile Ala Leu Glu Ser Pro Tyr Glu Ile Val Glu Lys
   290                 295                 300

ACC GCA AAG GTT TAC CAA AAA AGA AGA GAC GTT CTG GTG GAA GGG TTA          960
```

```
Thr Ala Lys Val Tyr Gln Lys Arg Arg Asp Val Leu Val Glu Gly Leu
305                 310                 315                 320

AAC AGG CTC GGC TGG AAA GTA AAA AAA CCT AAG GCT ACC ATG TTC GTC      1008
Asn Arg Leu Gly Trp Lys Val Lys Lys Pro Lys Ala Thr Met Phe Val
                325                 330                 335
TGG GCA AAG ATT CCC GAA TGG ATA AAT ATG AAC TCT CTG GAC TTT TCC      1056
Trp Ala Lys Ile Pro Glu Trp Ile Asn Met Asn Ser Leu Asp Phe Ser
            340                 345                 350

TTG TTC CTC CTA AAA GAG GCG AAG GTT GCG GTA TCC CCG GGT GTG GGC      1104
Leu Phe Leu Leu Lys Glu Ala Lys Val Ala Val Ser Pro Gly Val Gly
        355                 360                 365

TTT GGT CAG TAC GGA GAG GGG TAC GTA AGG TTT GCA CTT GTA GAA AAT      1152
Phe Gly Gln Tyr Gly Glu Gly Tyr Val Arg Phe Ala Leu Val Glu Asn
    370                 375                 380

GAA CAC AGG ATC AGA CAG GCT ATA AGG GGA ATA AGG AAA GCC TTC AGA      1200
Glu His Arg Ile Arg Gln Ala Ile Arg Gly Ile Arg Lys Ala Phe Arg
385                 390                 395                 400

AAA CTC CAG AAG GAG AGG AAA CTT GAA CCT GAG AGA AGT GCT TAA          1245
Lys Leu Gln Lys Glu Arg Lys Leu Glu Pro Glu Arg Ser Ala End
                405                 410                 414
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 1122 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: GENOMIC DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
ATG GAC AGG CTT GAA AAA GTA TCA CCC TTC ATA GTA ATG GAT ATC CTA       48
Met Asp Arg Leu Glu Lys Val Ser Pro Phe Ile Val Met Asp Ile Leu
                5                   10                  15

GCT CAG GCC CAG AAG TAC GAA GAC GTA GTA CAC ATG GAG ATA GGA GAG       96
Ala Gln Ala Gln Lys Tyr Glu Asp Val Val His Met Glu Ile Gly Glu
            20                  25                  30

CCC GAT TTA GAA CCG TCT CCC AAG GTA ATG GAA GCT CTG GAA CGT GCG      144
Pro Asp Leu Glu Pro Ser Pro Lys Val Met Glu Ala Leu Glu Arg Ala
        35                  40                  45

GTG AAG GAA AAG ACG TTC TTC TAC ACC CCT GCT CTG GGA CTC TGG GAA      192
Val Lys Glu Lys Thr Phe Phe Tyr Thr Pro Ala Leu Gly Leu Trp Glu
    50                  55                  60

CTC AGG GAA AGG ATA TCG GAG TTT TAC AGG AAA AAG TAC AGC GTT GAA      240
Leu Arg Glu Arg Ile Ser Glu Phe Tyr Arg Lys Lys Tyr Ser Val Glu
65                  70                  75                  80

GTT TCT CCA GAG AGA GTC ATC GTA ACT ACC GGA ACT TCG GGA GCG TTT      288
Val Ser Pro Glu Arg Val Ile Val Thr Thr Gly Thr Ser Gly Ala Phe
                85                  90                  95

CTC GTA GCC TAC GCC GTA ACA CTA AAT GCG GGA GAG AAG ATA ATC CTC      336
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Leu Val Ala Tyr Ala Val Thr Leu Asn Ala Gly Glu Lys Ile Ile Leu
            100                 105                 110

CCA GAC CCC TCT TAC CCC TGT TAC AAA AAC TTT GCC TAC CTC TTA GAC        384
Pro Asp Pro Ser Tyr Pro Cys Tyr Lys Asn Phe Ala Tyr Leu Leu Asp
        115                 120                 125

GCT CAG CCG GTT TTC GTA AAC GTT GAC AAG GAA ACG AAT TAC GAA GTA        432
Ala Gln Pro Val Phe Val Asn Val Asp Lys Glu Thr Asn Tyr Glu Val
    130                 135                 140

AGG AAA GAG ATG ATA GAA GAC ATT GAT GCG AAA GCC CTT CAC ATT TCC        480
Arg Lys Glu Met Ile Glu Asp Ile Asp Ala Lys Ala Leu His Ile Ser
145                 150                 155                 160

TCG CCT CAA AAC CCT ACG GGC ACA CTC TAC TCA CCT GAA ACC CTG AAG        528
Ser Pro Gln Asn Pro Thr Gly Thr Leu Tyr Ser Pro Glu Thr Leu Lys
                165                 170                 175

GAA CTT GCG GAG TAC TGC GAA GAG AAG GGT ATG TAC TTC ATA TCC GAC        576
Glu Leu Ala Glu Tyr Cys Glu Glu Lys Gly Met Tyr Phe Ile Ser Asp
            180                 185                 190

GAG ATT TAC CAC GGA CTC GTT TAC GAA GGT AGG GAG CAC ACA GCA CTT        624
Glu Ile Tyr His Gly Leu Val Tyr Glu Gly Arg Glu His Thr Ala Leu
        195                 200                 205
GAG TTC TCT GAC AGG GCT ATT GTC ATA AAC GGG TTT TCT AAG TAC TTC        672
Glu Phe Ser Asp Arg Ala Ile Val Ile Asn Gly Phe Ser Lys Tyr Phe
    210                 215                 220

TGT ATG CCA GGT TTC AGG ATA GGG TGG ATG ATA GTT CCG GAA GAA CTC        720
Cys Met Pro Gly Phe Arg Ile Gly Trp Met Ile Val Pro Glu Glu Leu
225                 230                 235                 240

GTG AGA AAG GCG GAA ATA GTA ATT CAG AAC GTA TTT ATA TCT GCC CCG        768
Val Arg Lys Ala Glu Ile Val Ile Gln Asn Val Phe Ile Ser Ala Pro
                245                 250                 255

ACG CTC AGT CAG TAC GCC GCC CTT GAG GCT TTT GAT TAC GAG TAT TTG        816
Thr Leu Ser Gln Tyr Ala Ala Leu Glu Ala Phe Asp Tyr Glu Tyr Leu
            260                 265                 270

GAG AAG GTA AGA AAA ACC TTT GAA GAG AGG AGG AAC TTC CTT TAT GGG        864
Glu Lys Val Arg Lys Thr Phe Glu Glu Arg Arg Asn Phe Leu Tyr Gly
        275                 280                 285

GAA CTG AAA AAA CTC TTC AAG ATA GAC GCG AAA CCT CAG GGA GCT TTT        912
Glu Leu Lys Lys Leu Phe Lys Ile Asp Ala Lys Pro Gln Gly Ala Phe
    290                 295                 300

TAC GTA TGG GCA AAC ATA AGT GAT TAC TCC ACA GAT AGC TAC GAA TTT        960
Tyr Val Trp Ala Asn Ile Ser Asp Tyr Ser Thr Asp Ser Tyr Glu Phe
305                 310                 315                 320

GCT TTA AAA CTT TTA AGG GAG GCG AGG GTG GCG GTA ACG CCC GGG GTG       1008
Ala Leu Lys Leu Leu Arg Glu Ala Arg Val Ala Val Thr Pro Gly Val
                325                 330                 335

GAC TTT GGA AAA AAC AAA ACG AAG GAG TAT ATA AGG TTT GCT TAT ACG       1056
Asp Phe Gly Lys Asn Lys Thr Lys Glu Tyr Ile Arg Phe Ala Tyr Thr
            340                 345                 350
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AGA AAG ATA GAA GAA CTT AAG GAG GGC GTT GAA AGG ATA AAG AAG TTC        1104
Arg Lys Ile Glu Glu Leu Lys Glu Gly Val Glu Arg Ile Lys Lys Phe
        355                 360                 365

TTA GAG AAG CTT AGC TGA                                            1122
Leu Glu Lys Leu Ser End
    370
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 1359 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: GENOMIC DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
ATG TGG GAA TTA GAC CCT AAA ACG CTC GAA AAG TGG GAC AAG GAG TAC          48
Met Trp Glu Leu Asp Pro Lys Thr Leu Glu Lys Trp Asp Lys Glu Tyr
                  5                  10                  15

TTC TGG CAT CCA TTT ACC CAG ATG AAA GTC TAC AGA GAA GAA GAA AAC          96
Phe Trp His Pro Phe Thr Gln Met Lys Val Tyr Arg Glu Glu Glu Asn
             20                  25                  30

CTG ATA TTT GAA CGC GGA GAA GGC GTT TAC CTG TGG GAC ATA TAC GGC         144
Leu Ile Phe Glu Arg Gly Glu Gly Val Tyr Leu Trp Asp Ile Tyr Gly
         35                  40                  45

AGG AAG TAT ATA GAT GCC ATA TCT TCC CTC TGG TGC AAC GTC CAC GGA         192
Arg Lys Tyr Ile Asp Ala Ile Ser Ser Leu Trp Cys Asn Val His Gly
     50                  55                  60

CAT AAC CAC CCT AAA CTG AAC AAC GCA GTT ATG AAA CAG CTC TGT AAG         240
His Asn His Pro Lys Leu Asn Asn Ala Val Met Lys Gln Leu Cys Lys
 65                  70                  75                  80

GTA GCT CAC ACA ACT ACT CTG GGA AGT TCC AAC GTT CCC GCC ATA CTC         288
Val Ala His Thr Thr Thr Leu Gly Ser Ser Asn Val Pro Ala Ile Leu
                 85                  90                  95

CTT GCA AAG AAG CTT GTA GAA ATT TCT CCT GAA GGA TTA AAC AAG GTC         336
Leu Ala Lys Lys Leu Val Glu Ile Ser Pro Glu Gly Leu Asn Lys Val
            100                 105                 110

TTT TAC TCC GAA GAC GGT GCG GAA GCA GTA GAG ATA GCG ATA AAG ATG         384
Phe Tyr Ser Glu Asp Gly Ala Glu Ala Val Glu Ile Ala Ile Lys Met
        115                 120                 125

GCT TAT CAC TAC TGG AAG AAC AAG GGA GTT AAA GGG AAA AAC GTT TTC         432
Ala Tyr His Tyr Trp Lys Asn Lys Gly Val Lys Gly Lys Asn Val Phe
    130                 135                 140

ATA ACG CTT TCC GAA GCC TAC CAC GGG GAT ACT GTA GGA GCG GTT AGC         480
Ile Thr Leu Ser Glu Ala Tyr His Gly Asp Thr Val Gly Ala Val Ser
145                 150                 155                 160

GTA GGG GGT ATA GAA CTC TTC CAC GGA ACT TAT AAA GAT CTC CTT TTC         528
Val Gly Gly Ile Glu Leu Phe His Gly Thr Tyr Lys Asp Leu Leu Phe
                165                 170                 175
```

```
AAG ACT ATA AAA CTC CCA TCT CCT TAC CTG TAC TGC AAG GAA AAG TAC          576
Lys Thr Ile Lys Leu Pro Ser Pro Tyr Leu Tyr Cys Lys Glu Lys Tyr
            180                 185                 190

GGG GAA CTC TGC CCT GAG TGC ACG GCA GAT TTA TTA AAA CAA CTG GAA          624
Gly Glu Leu Cys Pro Glu Cys Thr Ala Asp Leu Leu Lys Gln Leu Glu
        195                 200                 205

GAT ATC CTG AAG TCG CGG GAA GAT ATC GTT GCG GTC ATT ATG GAA GCG          672
Asp Ile Leu Lys Ser Arg Glu Asp Ile Val Ala Val Ile Met Glu Ala
    210                 215                 220

GGA ATT CAG GCA GCC GCG GGA ATG CTC CCC TTC CCT CCG GGA TTT TTG          720
Gly Ile Gln Ala Ala Ala Gly Met Leu Pro Phe Pro Pro Gly Phe Leu
225                 230                 235                 240

AAA GGC GTA AGG GAG CTT ACG AAG AAA TAC GAC ACT TTA ATG ATA GTT          768
Lys Gly Val Arg Glu Leu Thr Lys Lys Tyr Asp Thr Leu Met Ile Val
                245                 250                 255

GAC GAG GTT GCC ACG GGA TTT GGC AGG ACG GGA ACG ATG TTT TAC TGT          816
Asp Glu Val Ala Thr Gly Phe Gly Arg Thr Gly Thr Met Phe Tyr Cys
            260                 265                 270

GAG CAG GAA GGA GTC AGT CCG GAC TTT ATG TGT CTA GGT AAG GGT ATA          864
Glu Gln Glu Gly Val Ser Pro Asp Phe Met Cys Leu Gly Lys Gly Ile
        275                 280                 285

ACC GGA GGG TAC CTC CCG CTT GCT GCG ACA CTC ACA ACG GAC GAG GTG          912
Thr Gly Gly Tyr Leu Pro Leu Ala Ala Thr Leu Thr Thr Asp Glu Val
    290                 295                 300

TTC AAT GCC TTT TTA GGT GAG TTC GGG GAG GCA AAG CAC TTT TAC CAC          960
Phe Asn Ala Phe Leu Gly Glu Phe Gly Glu Ala Lys His Phe Tyr His
305                 310                 315                 320

GGG CAC ACC TAC ACT GGA AAT AAC CTC GCC TGT TCC GTT GCA CTC GCA         1008
Gly His Thr Tyr Thr Gly Asn Asn Leu Ala Cys Ser Val Ala Leu Ala
                325                 330                 335

AAC TTA GAA GTT TTT GAG GAA GAA AGA ACT TTA GAG AAG CTC CAA CCA         1056
Asn Leu Glu Val Phe Glu Glu Glu Arg Thr Leu Glu Lys Leu Gln Pro
            340                 345                 350

AAG ATA AAG CTT TTA AAG GAA AGG CTT CAG GAG TTC TGG GAA CTC AAG         1104
Lys Ile Lys Leu Leu Lys Glu Arg Leu Gln Glu Phe Trp Glu Leu Lys
        355                 360                 365

CAC GTT GGA GAT GTT AGA CAG CTA GGT TTT ATG GCT GGA ATA GAG CTG         1152
His Val Gly Asp Val Arg Gln Leu Gly Phe Met Ala Gly Ile Glu Leu
    370                 375                 380

GTG AAG GAC AAA GAA AAG GGA GAA CCT TTC CCT TAC GGT GAA AGG ACG         1200
Val Lys Asp Lys Glu Lys Gly Glu Pro Phe Pro Tyr Gly Glu Arg Thr
385                 390                 395                 400

GGA TTT AAG GTG GCT TAC AAG TGC AGG GAA AAA GGG GTG TTT TTG AGA         1245
Gly Phe Lys Val Ala Tyr Lys Cys Arg Glu Lys Gly Val Phe Leu Arg
                405                 410                 415

CCG CTC GGA GAC GTT ATG GTA TTG ATG ATG CCT CTT GTA ATA GAG GAA         1293
Pro Leu Gly Asp Val Met Val Leu Met Met Pro Leu Val Ile Glu Glu
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            420                 425                 430

GAC GAA ATG AAC TAC GTT ATT GAT ACA CTT AAA TGG GCA ATT AAA GAG      1341
Asp Glu Met Asn Tyr Val Ile Asp Thr Leu Lys Trp Ala Ile Lys Glu
        435                 440                 445

CTT GAA AAA GAG GTG TAG                                              1359
Leu Glu Lys Glu Val End
    450
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS
- (A) LENGTH: 1032 NUCLEOTIDES
- (B) TYPE: NUCLEIC ACID
- (C) STRANDEDNESS: SINGLE
- (D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: GENOMIC DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
ATG ACA TAC TTA ATG AAC AAT TAC GCA AGG TTG CCC GTA AAG TTT GTA       48
Met Thr Tyr Leu Met Asn Asn Tyr Ala Arg Leu Pro Val Lys Phe Val
                  5                  10                  15

AGG GGA AAA GGT GTT TAC CTG TAC GAT GAG GAA GGA AAG GAG TAT CTT       96
Arg Gly Lys Gly Val Tyr Leu Tyr Asp Glu Glu Gly Lys Glu Tyr Leu
            20                  25                  30

GAC TTT GTC TCC GGT ATA GGC GTC AAC TCC CTC GGT CAC GCT TAC CCA      144
Asp Phe Val Ser Gly Ile Gly Val Asn Ser Leu Gly His Ala Tyr Pro
        35                  40                  45

AAA CTC ACA GAA GCT CTA AAA GAA CAG GTT GAG AAA CTC CTC CAC GTT      192
Lys Leu Thr Glu Ala Leu Lys Glu Gln Val Glu Lys Leu Leu His Val
    50                  55                  60

TCA AAT CTT TAC GAA AAC CCG TGG CAG GAA GAA CTG GCT CAC AAA CTT      240
Ser Asn Leu Tyr Glu Asn Pro Trp Gln Glu Glu Leu Ala His Lys Leu
65                  70                  75                  80

GTA AAA CAC TTC TGG ACA GAA GGG AAG GTA TTT TTC GCA AAC AGC GGA      288
Val Lys His Phe Trp Thr Glu Gly Lys Val Phe Phe Ala Asn Ser Gly
                85                  90                  95

ACG GAA AGT GTA GAG GCG GCT ATA AAG CTC GCA AGG AAG TAC TGG AGG      336
Thr Glu Ser Val Glu Ala Ala Ile Lys Leu Ala Arg Lys Tyr Trp Arg
            100                 105                 110

GAT AAA GGA AAG AAC AAG TGG AAG TTT ATA TCC TTT GAA AAC TCT TTC      384
Asp Lys Gly Lys Asn Lys Trp Lys Phe Ile Ser Phe Glu Asn Ser Phe
        115                 120                 125

CAC GGG AGA ACC TAC GGT AGC CTC TCC GCA ACG GGA CAG CCA AAG TTC      432
His Gly Arg Thr Tyr Gly Ser Leu Ser Ala Thr Gly Gln Pro Lys Phe
    130                 135                 140

CAC AAA GGC TTT GAA CCT CTA GTT CCT GGA TTT TCT TAC GCA AAG CTG      480
His Lys Gly Phe Glu Pro Leu Val Pro Gly Phe Ser Tyr Ala Lys Leu
145                 150                 155                 160

AAC GAT ATA GAC AGC GTT TAC AAA CTC CTA GAC GAG GAA ACC GCG GGG      528
```

```
Asn Asp Ile Asp Ser Val Tyr Lys Leu Leu Asp Glu Glu Thr Ala Gly
                  165                 170                 175

ATA ATT ATT GAA GTT ATA CAA GGA GAG GGC GGA GTA AAC GAG GCG AGT        576
Ile Ile Ile Glu Val Ile Gln Gly Glu Gly Gly Val Asn Glu Ala Ser
            180                 185                 190

GAG GAT TTT CTA AGT AAA CTC CAG GAA ATT TGT AAA GAA AAA GAT GTG        624
Glu Asp Phe Leu Ser Lys Leu Gln Glu Ile Cys Lys Glu Lys Asp Val
        195                 200                 205

CTC TTA ATT ATA GAC GAA GTG CAA ACG GGA ATA GGA AGG ACC GGG GAA        672
Leu Leu Ile Ile Asp Glu Val Gln Thr Gly Ile Gly Arg Thr Gly Glu
    210                 215                 220

TTC TAC GCA TAT CAA CAC TTC AAT CTA AAA CCG GAC GTA ATT GCG CTT        720
Phe Tyr Ala Tyr Gln His Phe Asn Leu Lys Pro Asp Val Ile Ala Leu
225                 230                 235                 240

GCG AAG GGA CTC GGA GGA GGT GTG CCA ATA GGT GCC ATC CTT GCA AGG        768
Ala Lys Gly Leu Gly Gly Gly Val Pro Ile Gly Ala Ile Leu Ala Arg
                245                 250                 255

GAA GAA GTG GCC CAG AGC TTT ACT CCC GGC TCC CAC GGC TCT ACC TTC        816
Glu Glu Val Ala Gln Ser Phe Thr Pro Gly Ser His Gly Ser Thr Phe
            260                 265                 270

GGA GGA AAC CCC TTA GCC TGC AGG GCG GGA ACA GTG GTA GTA GAT GAA        864
Gly Gly Asn Pro Leu Ala Cys Arg Ala Gly Thr Val Val Val Asp Glu
        275                 280                 285

GTT GAA AAA CTC CTG CCT CAC GTA AGG GAA GTG GGG AAT TAC TTC AAA        912
Val Glu Lys Leu Leu Pro His Val Arg Glu Val Gly Asn Tyr Phe Lys
    290                 295                 300

GAA AAA CTG AAG GAA CTC GGC AAA GGA AAG GTA AAG GGA AGA GGA TTG        960
Glu Lys Leu Lys Glu Leu Gly Lys Gly Lys Val Lys Gly Arg Gly Leu
305                 310                 315                 320

ATG CTC GGT CTT GAA CTT GAA AGA GAG TGT AAA GAT TAC GTT CTC AAG       1008
Met Leu Gly Leu Glu Leu Glu Arg Glu Cys Lys Asp Tyr Val Leu Lys
                325                 330                 335

GCT CTT GAA AGG GAC TTC TCA TAA                                      1032
Ala Leu Glu Arg Asp Phe Ser End
            340
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 1197 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: GENOMIC DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
ATG CGG AAA CTG GCC GAG CGG GCG CAG AAA CTG AGC CCC TCT CCC ACC         48
Met Arg Lys Leu Ala Glu Arg Ala Gln Lys Leu Ser Pro Ser Pro Thr
                5                   10                  15
```

```
CTC TCG GTG GAC ACC AAG GCC AAG GAG CTT TTG CGG CAG GGG GAA AGG          96
Leu Ser Val Asp Thr Lys Ala Lys Glu Leu Leu Arg Gln Gly Glu Arg
            20                  25                  30

GTC ATC AAT TTC GGG GCG GGG GAG CCG GAC TTC GAT ACA CCG GAA CAC         144
Val Ile Asn Phe Gly Ala Gly Glu Pro Asp Phe Asp Thr Pro Glu His
        35                  40                  45

ATC AAG GAA GCG GCG AAG CGA GCT TTA GAT CAG GGC TTC ACC AAG TAC         192
Ile Lys Glu Ala Ala Lys Arg Ala Leu Asp Gln Gly Phe Thr Lys Tyr
    50                  55                  60

ACG CCG GTG GCT GGG ATC TTA CCT CTT CGG GAG GCC ATA TGC GAG AAG         240
Thr Pro Val Ala Gly Ile Leu Pro Leu Arg Glu Ala Ile Cys Glu Lys
65                  70                  75                  80

CTT TAC CGC GAC AAT CAA CTG GAA TAC AGC CCG AAT GAG ATC GTG GTC         288
Leu Tyr Arg Asp Asn Gln Leu Glu Tyr Ser Pro Asn Glu Ile Val Val
                85                  90                  95

TCC TGT GGC GCC AAG CAT TCT ATT TTC AAC GCT CTG CAG GTC CTC CTG         336
Ser Cys Gly Ala Lys His Ser Ile Phe Asn Ala Leu Gln Val Leu Leu
            100                 105                 110

GAC CCG GGG GAC GAG GTG ATA ATC CCC GTC CCC TAC TGG ACT TCC TAT         384
Asp Pro Gly Asp Glu Val Ile Ile Pro Val Pro Tyr Trp Thr Ser Tyr
        115                 120                 125

CCG GAG CAG GTG AAG CTG GCG GGA GGG GTG CCG GTT TTC GTC CCC ACC         432
Pro Glu Gln Val Lys Leu Ala Gly Gly Val Pro Val Phe Val Pro Thr
    130                 135                 140

TCT CCC GAG AAC GAC TTC AAG CTC AGG CCG GAA GAT CTA CGT GCG GCT         480
Ser Pro Glu Asn Asp Phe Lys Leu Arg Pro Glu Asp Leu Arg Ala Ala
145                 150                 155                 160

GTA ACC CCG CGC ACC CGC CTT TTG ATC CTC AAT TCC CCG GCC AAC CCC         528
Val Thr Pro Arg Thr Arg Leu Leu Ile Leu Asn Ser Pro Ala Asn Pro
                165                 170                 175

ACA GGC ACC GTT TAC CGC CGG GAG GAA CTT ATC GGC TTA GCG GAG GTA         576
Thr Gly Thr Val Tyr Arg Arg Glu Glu Leu Ile Gly Leu Ala Glu Val
            180                 185                 190

GCC CTG GAG GCC GAC CTA TGG ATC TTG TCG GAC GAG ATC TAC GAA AAG         624
Ala Leu Glu Ala Asp Leu Trp Ile Leu Ser Asp Glu Ile Tyr Glu Lys
        195                 200                 205

CTG ATC TAC GAC GGG ATG GAG CAC GTG AGC ATA GCC GCG CTC GAC CCG         672
Leu Ile Tyr Asp Gly Met Glu His Val Ser Ile Ala Ala Leu Asp Pro
    210                 215                 220

GAG GTC AAA AAG CGC ACG ATT GTG GTA AAC GGT GTT TCC AAG GCT TAC         720
Glu Val Lys Lys Arg Thr Ile Val Val Asn Gly Val Ser Lys Ala Tyr
225                 230                 235                 240

GCC ATG ACC GGT TGG CGC ATA GGT TAT GCT GCC GCT CCC CGG CCG ATA         768
Ala Met Thr Gly Trp Arg Ile Gly Tyr Ala Ala Ala Pro Arg Pro Ile
                245                 250                 255

GCC CAG GCC ATG ACC AAC CTC CAA AGC CAC AGT ACC TCT AAC CCC ACT         816
Ala Gln Ala Met Thr Asn Leu Gln Ser His Ser Thr Ser Asn Pro Thr
```

```
            260                 265                 270

TCC GTA GCC CAG GCG GCG GCG CTG GCC GCT CTG AAG GGG CCA CAA GAG        864
Ser Val Ala Gln Ala Ala Ala Leu Ala Ala Leu Lys Gly Pro Gln Glu
        275                 280                 285

CCG GTG GAG AAC ATG CGC CGG GCT TTT CAA AAG CGG CGG GAT TTC ATC        912
Pro Val Glu Asn Met Arg Arg Ala Phe Gln Lys Arg Arg Asp Phe Ile
    290                 295                 300

TGG CAG TAC CTA AAC TCC TTA CCC GGA GTG CGC TGC CCC AAA CCT TTA        960
Trp Gln Tyr Leu Asn Ser Leu Pro Gly Val Arg Cys Pro Lys Pro Leu
305                 310                 315                 320

GGG GCC TTT TAC GTC TTT CCA GAA GTT GAG CGG GCT TTT GGG CCG CCG       1008
Gly Ala Phe Tyr Val Phe Pro Glu Val Glu Arg Ala Phe Gly Pro Pro
                325                 330                 335

TCT AAA AGG ACG GGA AAT ACT ACC GCT AGC GAC CTG GCC CTT TTC CTC       1056
Ser Lys Arg Thr Gly Asn Thr Thr Ala Ser Asp Leu Ala Leu Phe Leu
            340                 345                 350

CTG GAA GAG ATA AAA GTG GCC ACC GTG GCT GGG GCT GCC TTT GGG GAC       1104
Leu Glu Glu Ile Lys Val Ala Thr Val Ala Gly Ala Ala Phe Gly Asp
        355                 360                 365

GAT CGC TAC CTG CGC TTT TCC TAC GCC CTG CGG CTG GAA GAT ATC GAA       1152
Asp Arg Tyr Leu Arg Phe Ser Tyr Ala Leu Arg Leu Glu Asp Ile Glu
    370                 375                 380

GAG GGG ATG CAA CGG TTT AAA GAA TTG ATC GAA GCG GCA CTT TAA           1197
Glu Gly Met Gln Arg Phe Lys Glu Leu Ile Glu Ala Ala Leu End
385                 390                 395
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 1779 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: GENOMIC DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
ATG TGC GGG ATA GTC GGA TAC GTA GGG AGG GAT TTA GCC CTT CCT ATA         48
Met Cys Gly Ile Val Gly Tyr Val Gly Arg Asp Leu Ala Leu Pro Ile
                5                   10                  15

GTC CTC GGA GCT CTT GAG AGA CTC GAA TAC AGG GGT TAC GAC TCC GCG         96
Val Leu Gly Ala Leu Glu Arg Leu Glu Tyr Arg Gly Tyr Asp Ser Ala
            20                  25                  30

GGA GTT GCC CTT ATA GAA GAC GGG AAA CTC ATA GTT GAA AAG AAG AAG        144
Gly Val Ala Leu Ile Glu Asp Gly Lys Leu Ile Val Glu Lys Lys Lys
        35                  40                  45

GGA AAG ATA AGG GAA CTC GTT AAA GCG CTA TGG GGA AAG GAT TAC AAG        192
Gly Lys Ile Arg Glu Leu Val Lys Ala Leu Trp Gly Lys Asp Tyr Lys
    50                  55                  60
```

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GCT AAA ACG GGT ATA GGT CAC ACA CGC TGG GCA ACC CAC GGA AAG CCC          240
Ala Lys Thr Gly Ile Gly His Thr Arg Trp Ala Thr His Gly Lys Pro
 65                  70                  75                  80

ACG GAC GAG AAC GCC CAC CCC CAC ACC GAC GAA AAA GGT GAG TTT GCA          288
Thr Asp Glu Asn Ala His Pro His Thr Asp Glu Lys Gly Glu Phe Ala
                 85                  90                  95

GTA GTT CAC AAC GGG ATA ATA GAA AAC TAC TTA GAA CTA AAA GAG GAA          336
Val Val His Asn Gly Ile Ile Glu Asn Tyr Leu Glu Leu Lys Glu Glu
            100                 105                 110

CTA AAG AAG GAA GGT GTA AAG TTC AGG TCC GAA ACA GAC ACA GAA GTT          384
Leu Lys Lys Glu Gly Val Lys Phe Arg Ser Glu Thr Asp Thr Glu Val
        115                 120                 125

ATA GCC CAC CTC ATA GCG AAG AAC TAC AGG GGG GAC TTA CTG GAG GCC          432
Ile Ala His Leu Ile Ala Lys Asn Tyr Arg Gly Asp Leu Leu Glu Ala
    130                 135                 140

GTT TTA AAA ACC GTA AAG AAA TTA AAG GGT GCT TTT GCC TTT GCG GTT          480
Val Leu Lys Thr Val Lys Lys Leu Lys Gly Ala Phe Ala Phe Ala Val
145                 150                 155                 160

ATA ACG GTT CAC GAA CCA AAC AGA CTA ATA GGA GTG AAG CAG GGG AGT          528
Ile Thr Val His Glu Pro Asn Arg Leu Ile Gly Val Lys Gln Gly Ser
                165                 170                 175

CCT TTA ATC GTC GGA CTC GGA GAA GGA GAA AAC TTC CTC GCT TCA GAT          576
Pro Leu Ile Val Gly Leu Gly Glu Gly Glu Asn Phe Leu Ala Ser Asp
            180                 185                 190

ATT CCC GCA ATA CTT CCT TAC ACG AAA AAG ATT ATT GTT CTT GAT GAC          624
Ile Pro Ala Ile Leu Pro Tyr Thr Lys Lys Ile Ile Val Leu Asp Asp
        195                 200                 205

GGG GAA ATA GCG GAC CTG ACT CCC GAC ACT GTG AAC ATT TAC AAC TTT          672
Gly Glu Ile Ala Asp Leu Thr Pro Asp Thr Val Asn Ile Tyr Asn Phe
    210                 215                 220

GAG GGA GAG CCC GTT TCA AAG GAA GTA ATG ATT ACG CCC TGG GAT CTT          720
Glu Gly Glu Pro Val Ser Lys Glu Val Met Ile Thr Pro Trp Asp Leu
225                 230                 235                 240

GTT TCT GCG GAA AAG GGT GGT TTT AAA CAC TTC ATG CTA AAA GAG ATA          768
Val Ser Ala Glu Lys Gly Gly Phe Lys His Phe Met Leu Lys Glu Ile
                245                 250                 255

TAC GAA CAG CCC AAA GCC ATA AAC GAC ACA CTC AAG GGT TTC CTC TCA          816
Tyr Glu Gln Pro Lys Ala Ile Asn Asp Thr Leu Lys Gly Phe Leu Ser
            260                 265                 270

ACC GAA GAC GCA ATA CCC TTT AAG TTA AAA GAC TTC AGA AGG GTT TTA          864
Thr Glu Asp Ala Ile Pro Phe Lys Leu Lys Asp Phe Arg Arg Val Leu
        275                 280                 285

ATA ATA GCG TGC GGG ACC TCT TAC CAC GCG GGC TTC GTC GGA AAG TAC          912
Ile Ile Ala Cys Gly Thr Ser Tyr His Ala Gly Phe Val Gly Lys Tyr
    290                 295                 300

TGG ATA GAG AGA TTT GCA GGT GTT CCC ACA GAG GTA ATT TAC GCT TCG          960
Trp Ile Glu Arg Phe Ala Gly Val Pro Thr Glu Val Ile Tyr Ala Ser
```

```
305                 310                 315                 320

GAA TTC AGG TAT GCG GAC GTT CCC GTT TCG GAC AAG GAT ATC GTT ATC      1008
Glu Phe Arg Tyr Ala Asp Val Pro Val Ser Asp Lys Asp Ile Val Ile
                325                 330                 335

GGA ATT TCC CAG TCA GGA GAG ACC GCT GAC ACA AAG TTT GCC CTT CAG      1056
Gly Ile Ser Gln Ser Gly Glu Thr Ala Asp Thr Lys Phe Ala Leu Gln
            340                 345                 350

TCC GCA AAG GAA AAG GGA GCC TTT ACC GTG GGA CTC GTA AAC GTA GTG      1104
Ser Ala Lys Glu Lys Gly Ala Phe Thr Val Gly Leu Val Asn Val Val
        355                 360                 365

GGA AGT GCC ATA GAC AGG GAG TCG GAC TTT TCC CTT CAC ACA CAT GCG      1152
Gly Ser Ala Ile Asp Arg Glu Ser Asp Phe Ser Leu His Thr His Ala
    370                 375                 380
GGA CCC GAA ATA GGC GTG GCG GCT ACA AAG ACC TTC ACC GCA CAG TTC      1200
Gly Pro Glu Ile Gly Val Ala Ala Thr Lys Thr Phe Thr Ala Gln Phe
385                 390                 395                 400

ACC GCA CTC TAC GCC CTT TCG GTA AGG GAA AGT GAG GAG AGG GAA AAT      1248
Thr Ala Leu Tyr Ala Leu Ser Val Arg Glu Ser Glu Glu Arg Glu Asn
                405                 410                 415

CTA ATA AGA CTC CTT GAA AAG GTT CCA TCA CTC GTT GAA CAA ACA CTG      1296
Leu Ile Arg Leu Leu Glu Lys Val Pro Ser Leu Val Glu Gln Thr Leu
            420                 425                 430

AAC ACC GCA GAA GAA GTG GAG AAG GTA GCG GAA AAG TAC ATG AAA AAG      1344
Asn Thr Ala Glu Glu Val Glu Lys Val Ala Glu Lys Tyr Met Lys Lys
        435                 440                 445

AAA AAC ATG CTT TAC CTC GGA AGG TAC TTA AAT TAC CCC ATA GCG CTG      1392
Lys Asn Met Leu Tyr Leu Gly Arg Tyr Leu Asn Tyr Pro Ile Ala Leu
    450                 455                 460

GAG GGA GCT CTT AAA CTT AAA GAA ATT TCT TAC ATA CAC GCG GAA GGT      1440
Glu Gly Ala Leu Lys Leu Lys Glu Ile Ser Tyr Ile His Ala Glu Gly
465                 470                 475                 480

TAT CCC GCA GGG GAG ATG AAG CAC GGT CCC ATA GCC CTC ATA GAC GAA      1488
Tyr Pro Ala Gly Glu Met Lys His Gly Pro Ile Ala Leu Ile Asp Glu
                485                 490                 495

AAC ATG CCG GTT GTG GTA ATC GCA CCG AAA GAC AGG GTT TAC GAG AAG      1536
Asn Met Pro Val Val Val Ile Ala Pro Lys Asp Arg Val Tyr Glu Lys
            500                 505                 510

ATA CTC TCA AAC GTA GAA GAG GTT CTC GCA AGA AAG GGA AGG GTT ATT      1584
Ile Leu Ser Asn Val Glu Glu Val Leu Ala Arg Lys Gly Arg Val Ile
        515                 520                 525

TCT GTA GGC TTT AAA GGA GAC GAA ACT CTC AAA AGC AAA TCC GAG AGC      1632
Ser Val Gly Phe Lys Gly Asp Glu Thr Leu Lys Ser Lys Ser Glu Ser
    530                 535                 540

GTT ATG GAA ATC CCG AAG GCA GAA GAA CCG ATA ACT CCT TTC TTG ACG      1680
Val Met Glu Ile Pro Lys Ala Glu Glu Pro Ile Thr Pro Phe Leu Thr
545                 550                 555                 560

GTA ATA CCC CTG CAA CTC TTT GCC TAC TTT ATA GCG AGC AAA CTG GGA      1728
Val Ile Pro Leu Gln Leu Phe Ala Tyr Phe Ile Ala Ser Lys Leu Gly
```

```
                565                 570                 575                 580

CTG GAT GTG GAT CAG CCG AGA AAT CTC GCC AAA ACG GTC ACG GTG GAA        1776
Leu Asp Val Asp Gln Pro Arg Asn Leu Ala Lys Thr Val Thr Val Glu
          580                 585                 590

TAA                                                                    1779
End
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 1065 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: GENOMIC DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
ATG ATA CCC CAG AGG ATT AAG GAA CTT GAA GCT TAC AAG ACG GAG GTC        48
Met Ile Pro Gln Arg Ile Lys Glu Leu Glu Ala Tyr Lys Thr Glu Val
                5                  10                  15

ACT CCC GCC TCC GTC AGG CTT TCC TCT AAC GAA TTC CCC TAC GAC TTT        96
Thr Pro Ala Ser Val Arg Leu Ser Ser Asn Glu Phe Pro Tyr Asp Phe
            20                  25                  30

CCC GAG GAG ATA AAA CAA AGG GCC TTA GAA GAA TTA AAA AAG GTT CCC       144
Pro Glu Glu Ile Lys Gln Arg Ala Leu Glu Glu Leu Lys Lys Val Pro
        35                  40                  45

TTG AAC AAA TAC CCA GAC CCC GAA GCG AAA GAG TTA AAA GCG GTT CTT       192
Leu Asn Lys Tyr Pro Asp Pro Glu Ala Lys Glu Leu Lys Ala Val Leu
    50                  55                  60

GCG GAT TTT TTC GGC GTT AAG GAA GAA AAT TTA GTT CTC GGT AAC GGT       240
Ala Asp Phe Phe Gly Val Lys Glu Glu Asn Leu Val Leu Gly Asn Gly
65                  70                  75                  80

TCG GAC GAA CTC ATA TAC TAC CTC TCA ATA GCT ATA GGT GAA CTT TAC       288
Ser Asp Glu Leu Ile Tyr Tyr Leu Ser Ile Ala Ile Gly Glu Leu Tyr
                85                  90                  95

ATA CCC GTT TAC ATA CCT GTT CCC ACC TTT CCC ATG TAC GAG ATA AGT       336
Ile Pro Val Tyr Ile Pro Val Pro Thr Phe Pro Met Tyr Glu Ile Ser
            100                 105                 110

GCG AAA GTT CTC GGA AGA CCC CTC GTA AAG GTT CAA CTG GAC GAA AAC       384
Ala Lys Val Leu Gly Arg Pro Leu Val Lys Val Gln Leu Asp Glu Asn
        115                 120                 125

TTT GAT ATA GAC TTA GAA AGA AGT ATT GAA TTA ATA GAG AAA GAA AAA       432
Phe Asp Ile Asp Leu Glu Arg Ser Ile Glu Leu Ile Glu Lys Glu Lys
    130                 135                 140

CCC GTT CTC GGG TAC TTT GCT TAC CCA AAC AAC CCC ACG GGA AAC CTC       480
Pro Val Leu Gly Tyr Phe Ala Tyr Pro Asn Asn Pro Thr Gly Asn Leu
145                 150                 155                 160

TTT TCC AGG GGA AAG ATT GAG GAG ATA AGA AAC AGG GGT GTT TTC TGT       528
Phe Ser Arg Gly Lys Ile Glu Glu Ile Arg Asn Arg Gly Val Phe Cys
```

```
                  165                 170                 175

GTA ATA GAC GAA GCC TAC TAT CAT TAC TCC GGA GAA ACC TTT CTG GAA          576
Val Ile Asp Glu Ala Tyr Tyr His Tyr Ser Gly Glu Thr Phe Leu Glu
            180                 185                 190

GAC GCG CTC AAA AGG GAA GAT ACG GTA GTT TTG AGG ACA CTT TCA AAA          624
Asp Ala Leu Lys Arg Glu Asp Thr Val Val Leu Arg Thr Leu Ser Lys
        195                 200                 205

ATC GGT ATG GCG AGT TTA AGG GTA GGG ATT TTA ATA GGG AAG GGG GAA          672
Ile Gly Met Ala Ser Leu Arg Val Gly Ile Leu Ile Gly Lys Gly Glu
    210                 215                 220

ATC GTC TCA GAA ATT AAC AAG GTG AGA CTC CCC TTC AAC GTG ACC TAC          720
Ile Val Ser Glu Ile Asn Lys Val Arg Leu Pro Phe Asn Val Thr Tyr
225                 230                 235                 240

CCC TCT CAG GTG ATG GCA AAA GTT CTC CTC ACG GAG GGA AGA GAA TTC          768
Pro Ser Gln Val Met Ala Lys Val Leu Leu Thr Glu Gly Arg Glu Phe
                245                 250                 255

CTA ATG GAA AAG ATA CAG GAG GTT GTA ACA GAG CGA GAA AGG ATG TAC          816
Leu Met Glu Lys Ile Gln Glu Val Val Thr Glu Arg Glu Arg Met Tyr
            260                 265                 270

GAC GAA ATG AAG AAA ATA GAA GGA GTT GAG GTT TTT CCG AGT AAG GCT          864
Asp Glu Met Lys Lys Ile Glu Gly Val Glu Val Phe Pro Ser Lys Ala
        275                 280                 285

AAC TTC TTG CTT TTC AGA ACG CCT TAC CCC GCC CAC GAG GTT TAT CAG          912
Asn Phe Leu Leu Phe Arg Thr Pro Tyr Pro Ala His Glu Val Tyr Gln
    290                 295                 300

GAG CTA CTG AAA AGG GAT GTC CTC GTC AGG AAC GTA TCT TAC ATG GAA          960
Glu Leu Leu Lys Arg Asp Val Leu Val Arg Asn Val Ser Tyr Met Glu
305                 310                 315                 320

GGA CTC CAA AAG TGC CTC AGG GTA AGC GTA GGG AAA CCG GAA GAA AAC         1008
Gly Leu Gln Lys Cys Leu Arg Val Ser Val Gly Lys Pro Glu Glu Asn
                325                 330                 335

AAC AAG TTT CTG GAA GCA CTG GAG GAG AGT ATA AAA TCC CTT TCA AGC         1056
Asn Lys Phe Leu Glu Ala Leu Glu Glu Ser Ile Lys Ser Leu Ser Ser
            340                 345                 350

TCT CTT TAA                                                             1065
Ser Leu End
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 912 NUCLEOTIDES
(B) TYPE: NUCLEIC ACID
(C) STRANDEDNESS: SINGLE
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: GENOMIC DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
ATG AAG CCG TAC GCT AAA TAT ATC TGG CTT GAC GGC AGA ATA CTT AAG          48
```

```
Met Lys Pro Tyr Ala Lys Tyr Ile Trp Leu Asp Gly Arg Ile Leu Lys
                  5                  10                  15

TGG GAA GAC GCG AAA ATA CAC GTG TTG ACT CAC GCG CTT CAC TAC GGA          96
Trp Glu Asp Ala Lys Ile His Val Leu Thr His Ala Leu His Tyr Gly
            20                  25                  30

ACC TCT ATA TTC GAG GGA ATA AGA GGG TAT TGG AAC GGC GAT AAT TTG         144
Thr Ser Ile Phe Glu Gly Ile Arg Gly Tyr Trp Asn Gly Asp Asn Leu
        35                  40                  45

CTC GTC TTT AGG TTA GAA GAA CAC ATC GAC CGC ATG TAC AGA TCG GCT         192
Leu Val Phe Arg Leu Glu Glu His Ile Asp Arg Met Tyr Arg Ser Ala
    50                  55                  60

AAG ATA CTA GGC ATA AAT ATT CCG TAT ACA AGA GAG GAA GTC CGC CAA         240
Lys Ile Leu Gly Ile Asn Ile Pro Tyr Thr Arg Glu Glu Val Arg Gln
65                  70                  75                  80

GCT GTA CTA GAG ACC ATA AAG GCT AAT AAC TTC CGA GAG GAT GTC TAC         288
Ala Val Leu Glu Thr Ile Lys Ala Asn Asn Phe Arg Glu Asp Val Tyr
                85                  90                  95

ATA AGA CCT GTG GCG TTT GTC GCC TCG CAG ACG GTG ACG CTT GAC ATA         336
Ile Arg Pro Val Ala Phe Val Ala Ser Gln Thr Val Thr Leu Asp Ile
            100                 105                 110

AGA AAT TTG GAA GTC TCC CTC GCG GTT ATT GTA TTC CCA TTT GGC AAA         384
Arg Asn Leu Glu Val Ser Leu Ala Val Ile Val Phe Pro Phe Gly Lys
        115                 120                 125

TAC CTC TCG CCC AAC GGC ATT AAG GCA ACG ATT GTA AGC TGG CGT AGA         432
Tyr Leu Ser Pro Asn Gly Ile Lys Ala Thr Ile Val Ser Trp Arg Arg
    130                 135                 140

GTA CAT AAT ACA ATG CTC CCT GTG ATG GCA AAA ATC GGC GGT ATA TAT         480
Val His Asn Thr Met Leu Pro Val Met Ala Lys Ile Gly Gly Ile Tyr
145                 150                 155                 160

GTA AAC TCT GTA CTT GCG CTT GTA GAG GCT AGA AGC AGG GGA TTT GAC         528
Val Asn Ser Val Leu Ala Leu Val Glu Ala Arg Ser Arg Gly Phe Asp
                165                 170                 175

GAG GCT TTA TTA ATG GAC GTT AAC GGT TAT GTT GTT GAG GGT TCT GGA         576
Glu Ala Leu Leu Met Asp Val Asn Gly Tyr Val Val Glu Gly Ser Gly
            180                 185                 190

GAG AAT ATT TTC ATT GTC AGA GGT GGA AGG CTT TTC ACG CCG CCA GTA         624
Glu Asn Ile Phe Ile Val Arg Gly Gly Arg Leu Phe Thr Pro Pro Val
        195                 200                 205

CAC GAA TCT ATC CTC GAG GGA ATT ACG AGG GAT ACG GTA ATA AAG CTC         672
His Glu Ser Ile Leu Glu Gly Ile Thr Arg Asp Thr Val Ile Lys Leu
    210                 215                 220

AGC GGG GAT GTG GGA CTT CGG GTG GAG GAA AAG CCT ATT ACG AGG GAG         720
Ser Gly Asp Val Gly Leu Arg Val Glu Glu Lys Pro Ile Thr Arg Glu
225                 230                 235                 240

GAG GTG TAT ACA GCC GAC GAG GTG TTT TTA GTA GGA ACC GCC GCA GAG         768
Glu Val Tyr Thr Ala Asp Glu Val Phe Leu Val Gly Thr Ala Ala Glu
                245                 250                 255
```

```
ATA ACG CCA GTG GTG GAG GTT GAC GGC AGA ACA ATC GGC ACA GGC AAG          816
Ile Thr Pro Val Val Glu Val Asp Gly Arg Thr Ile Gly Thr Gly Lys
            260                 265                 270

CCG GGC CCC ATT ACG ACA AAA ATA GCT GAG CTG TAC TCA AAC GTC GTG          864
Pro Gly Pro Ile Thr Thr Lys Ile Ala Glu Leu Tyr Ser Asn Val Val
        275                 280                 285

AGA GGC AAA GTA GAG AAA TAC TTA AAT TGG ATC ACT CCT GTG TAT TAG          912

Arg Gly Lys Val Glu Lys Tyr Leu Asn Trp Ile Thr Pro Val Tyr End
    290                 295                 300
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 414 AMINO ACIDS
(B) TYPE: AMINO ACID
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: PROTEIN

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
Met Ile Glu Asp Pro Met Asp Trp Ala Phe Pro Arg Ile Lys Arg Leu
                5                  10                  15

Pro Gln Tyr Val Phe Ser Leu Val Asn Glu Leu Lys Tyr Lys Leu Arg
            20                  25                  30

Arg Glu Gly Glu Asp Val Val Asp Leu Gly Met Gly Asn Pro Asn Met
        35                  40                  45

Pro Pro Ala Lys His Ile Ile Asp Lys Leu Cys Glu Val Ala Gln Lys
    50                  55                  60

Pro Asn Val His Gly Tyr Ser Ala Ser Arg Gly Ile Pro Arg Leu Arg
65                  70                  75                  80

Lys Ala Ile Cys Asn Phe Tyr Glu Glu Arg Tyr Gly Val Lys Leu Asp
                85                  90                  95

Pro Glu Arg Glu Ala Ile Leu Thr Ile Gly Ala Lys Glu Gly Tyr Ser
            100                 105                 110

His Leu Met Leu Ala Met Ile Ser Pro Gly Asp Thr Val Ile Val Pro
        115                 120                 125

Asn Pro Thr Tyr Pro Ile His Tyr Tyr Ala Pro Ile Ile Ala Gly Gly
    130                 135                 140

Glu Val His Ser Ile Pro Leu Asn Phe Ser Asp Asp Gln Asp His Gln
145                 150                 155                 160

Glu Glu Phe Leu Arg Arg Leu Tyr Glu Ile Val Lys Thr Ala Met Pro
                165                 170                 175

Lys Pro Lys Ala Val Val Ile Ser Phe Pro His Asn Pro Thr Thr Ile
            180                 185                 190

Thr Val Glu Lys Asp Phe Phe Lys Glu Ile Val Lys Phe Ala Lys Glu
        195                 200                 205
```

```
His Gly Leu Trp Ile Ile His Asp Phe Ala Tyr Ala Asp Ile Ala Phe
    210                 215                 220

Asp Gly Tyr Lys Pro Pro Ser Ile Leu Glu Ile Glu Gly Ala Lys Asp
225                 230                 235                 240

Val Ala Val Glu Leu Tyr Ser Met Ser Lys Gly Phe Ser Met Ala Gly
                245                 250                 255

Trp Arg Val Ala Phe Val Val Gly Asn Glu Ile Leu Ile Lys Asn Leu
            260                 265                 270

Ala His Leu Lys Ser Tyr Leu Asp Tyr Gly Ile Phe Thr Pro Ile Gln
        275                 280                 285

Val Ala Ser Ile Ile Ala Leu Glu Ser Pro Tyr Glu Ile Val Glu Lys
    290                 295                 300

Thr Ala Lys Val Tyr Gln Lys Arg Arg Asp Val Leu Val Glu Gly Leu
305                 310                 315                 320

Asn Arg Leu Gly Trp Lys Val Lys Lys Pro Lys Ala Thr Met Phe Val
                325                 330                 335
Trp Ala Lys Ile Pro Glu Trp Ile Asn Met Asn Ser Leu Asp Phe Ser
            340                 345                 350

Leu Phe Leu Leu Lys Glu Ala Lys Val Ala Val Ser Pro Gly Val Gly
        355                 360                 365

Phe Gly Gln Tyr Gly Glu Gly Tyr Val Arg Phe Ala Leu Val Glu Asn
    370                 375                 380

Glu His Arg Ile Arg Gln Ala Ile Arg Gly Ile Arg Lys Ala Phe Arg
385                 390                 395                 400

Lys Leu Gln Lys Glu Arg Lys Leu Glu Pro Glu Arg Ser Ala End
                405                 410             414
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 373 AMINO ACIDS
(B) TYPE: AMINO ACID
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: PROTEIN

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Met Asp Arg Leu Glu Lys Val Ser Pro Phe Ile Val Met Asp Ile Leu
                5                   10                  15

Ala Gln Ala Gln Lys Tyr Glu Asp Val Val His Met Glu Ile Gly Glu
            20                  25                  30

Pro Asp Leu Glu Pro Ser Pro Lys Val Met Glu Ala Leu Glu Arg Ala
        35                  40                  45

Val Lys Glu Lys Thr Phe Phe Tyr Thr Pro Ala Leu Gly Leu Trp Glu
    50                  55                  60

Leu Arg Glu Arg Ile Ser Glu Phe Tyr Arg Lys Lys Tyr Ser Val Glu
```

```
65                  70                  75                  80

Val Ser Pro Glu Arg Val Ile Val Thr Thr Gly Thr Ser Gly Ala Phe
                 85                  90                  95

Leu Val Ala Tyr Ala Val Thr Leu Asn Ala Gly Glu Lys Ile Ile Leu
            100                 105                 110

Pro Asp Pro Ser Tyr Pro Cys Tyr Lys Asn Phe Ala Tyr Leu Leu Asp
        115                 120                 125

Ala Gln Pro Val Phe Val Asn Val Asp Lys Glu Thr Asn Tyr Glu Val
    130                 135                 140

Arg Lys Glu Met Ile Glu Asp Ile Asp Ala Lys Ala Leu His Ile Ser
145                 150                 155                 160

Ser Pro Gln Asn Pro Thr Gly Thr Leu Tyr Ser Pro Glu Thr Leu Lys
                165                 170                 175

Glu Leu Ala Glu Tyr Cys Glu Glu Lys Gly Met Tyr Phe Ile Ser Asp
            180                 185                 190

Glu Ile Tyr His Gly Leu Val Tyr Glu Gly Arg Glu His Thr Ala Leu
        195                 200                 205
Glu Phe Ser Asp Arg Ala Ile Val Ile Asn Gly Phe Ser Lys Tyr Phe
    210                 215                 220

Cys Met Pro Gly Phe Arg Ile Gly Trp Met Ile Val Pro Glu Glu Leu
225                 230                 235                 240

Val Arg Lys Ala Glu Ile Val Ile Gln Asn Val Phe Ile Ser Ala Pro
                245                 250                 255

Thr Leu Ser Gln Tyr Ala Ala Leu Glu Ala Phe Asp Tyr Glu Tyr Leu
            260                 265                 270

Glu Lys Val Arg Lys Thr Phe Glu Glu Arg Arg Asn Phe Leu Tyr Gly
        275                 280                 285

Glu Leu Lys Lys Leu Phe Lys Ile Asp Ala Lys Pro Gln Gly Ala Phe
    290                 295                 300

Tyr Val Trp Ala Asn Ile Ser Asp Tyr Ser Thr Asp Ser Tyr Glu Phe
305                 310                 315                 320

Ala Leu Lys Leu Leu Arg Glu Ala Arg Val Ala Val Thr Pro Gly Val
                325                 330                 335

Asp Phe Gly Lys Asn Lys Thr Lys Glu Tyr Ile Arg Phe Ala Tyr Thr
            340                 345                 350

Arg Lys Ile Glu Glu Leu Lys Glu Gly Val Glu Arg Ile Lys Lys Phe
        355                 360                 365

Leu Glu Lys Leu Ser
    370
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 453 AMINO ACIDS
(B) TYPE: AMINO ACID
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: PROTEIN

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
Met Trp Glu Leu Asp Pro Lys Thr Leu Glu Lys Trp Asp Lys Glu Tyr
 1               5                  10                  15

Phe Trp His Pro Phe Thr Gln Met Lys Val Tyr Arg Glu Glu Glu Asn
            20                  25                  30

Leu Ile Phe Glu Arg Gly Glu Gly Val Tyr Leu Trp Asp Ile Tyr Gly
        35                  40                  45

Arg Lys Tyr Ile Asp Ala Ile Ser Ser Leu Trp Cys Asn Val His Gly
    50                  55                  60

His Asn His Pro Lys Leu Asn Asn Ala Val Met Lys Gln Leu Cys Lys
65                  70                  75                  80

Val Ala His Thr Thr Thr Leu Gly Ser Ser Asn Val Pro Ala Ile Leu
                85                  90                  95

Leu Ala Lys Lys Leu Val Glu Ile Ser Pro Glu Gly Leu Asn Lys Val
            100                 105                 110

Phe Tyr Ser Glu Asp Gly Ala Glu Ala Val Glu Ile Ala Ile Lys Met
        115                 120                 125

Ala Tyr His Tyr Trp Lys Asn Lys Gly Val Lys Gly Lys Asn Val Phe
    130                 135                 140

Ile Thr Leu Ser Glu Ala Tyr His Gly Asp Thr Val Gly Ala Val Ser
145                 150                 155                 160

Val Gly Gly Ile Glu Leu Phe His Gly Thr Tyr Lys Asp Leu Leu Phe
                165                 170                 175

Lys Thr Ile Lys Leu Pro Ser Pro Tyr Leu Tyr Cys Lys Glu Lys Tyr
            180                 185                 190

Gly Glu Leu Cys Pro Glu Cys Thr Ala Asp Leu Leu Lys Gln Leu Glu
        195                 200                 205

Asp Ile Leu Lys Ser Arg Glu Asp Ile Val Ala Val Ile Met Glu Ala
    210                 215                 220

Gly Ile Gln Ala Ala Ala Gly Met Leu Pro Phe Pro Pro Gly Phe Leu
225                 230                 235                 240

Lys Gly Val Arg Glu Leu Thr Lys Lys Tyr Asp Thr Leu Met Ile Val
                245                 250                 255

Asp Glu Val Ala Thr Gly Phe Gly Arg Thr Gly Thr Met Phe Tyr Cys
            260                 265                 270
```

```
Glu Gln Glu Gly Val Ser Pro Asp Phe Met Cys Leu Gly Lys Gly Ile
        275                 280                 285

Thr Gly Gly Tyr Leu Pro Leu Ala Ala Thr Leu Thr Thr Asp Glu Val
    290                 295                 300

Phe Asn Ala Phe Leu Gly Glu Phe Gly Glu Ala Lys His Phe Tyr His
305                 310                 315                 320

Gly His Thr Tyr Thr Gly Asn Asn Leu Ala Cys Ser Val Ala Leu Ala
                325                 330                 335

Asn Leu Glu Val Phe Glu Glu Glu Arg Thr Leu Glu Lys Leu Gln Pro
            340                 345                 350

Lys Ile Lys Leu Leu Lys Glu Arg Leu Gln Glu Phe Trp Glu Leu Lys
        355                 360                 365

His Val Gly Asp Val Arg Gln Leu Gly Phe Met Ala Gly Ile Glu Leu
    370                 375                 380

Val Lys Asp Lys Glu Lys Gly Glu Pro Phe Pro Tyr Gly Glu Arg Thr
385                 390                 395                 400

Gly Phe Lys Val Ala Tyr Lys Cys Arg Glu Lys Gly Val Phe Leu Arg
                405                 410                 415

Pro Leu Gly Asp Val Met Val Leu Met Met Pro Leu Val Ile Glu Glu
            420                 425                 430

Asp Glu Met Asn Tyr Val Ile Asp Thr Leu Lys Trp Ala Ile Lys Glu
        435                 440                 445

Leu Glu Lys Glu Val
    450
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 343 AMINO ACIDS
(B) TYPE: AMINO ACID
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: PROTEIN

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Met Thr Tyr Leu Met Asn Asn Tyr Ala Arg Leu Pro Val Lys Phe Val
                5                   10                  15

Arg Gly Lys Gly Val Tyr Leu Tyr Asp Glu Glu Gly Lys Glu Tyr Leu
            20                  25                  30

Asp Phe Val Ser Gly Ile Gly Val Asn Ser Leu Gly His Ala Tyr Pro
        35                  40                  45

Lys Leu Thr Glu Ala Leu Lys Glu Gln Val Glu Lys Leu Leu His Val
    50                  55                  60

Ser Asn Leu Tyr Glu Asn Pro Trp Gln Glu Glu Leu Ala His Lys Leu
65                  70                  75                  80
```

```
Val Lys His Phe Trp Thr Glu Gly Lys Val Phe Phe Ala Asn Ser Gly
                 85                  90                  95

Thr Glu Ser Val Glu Ala Ala Ile Lys Leu Ala Arg Lys Tyr Trp Arg
            100                 105                 110

Asp Lys Gly Lys Asn Lys Trp Lys Phe Ile Ser Phe Glu Asn Ser Phe
        115                 120                 125

His Gly Arg Thr Tyr Gly Ser Leu Ser Ala Thr Gly Gln Pro Lys Phe
    130                 135                 140

His Lys Gly Phe Glu Pro Leu Val Pro Gly Phe Ser Tyr Ala Lys Leu
145                 150                 155                 160

Asn Asp Ile Asp Ser Val Tyr Lys Leu Leu Asp Glu Glu Thr Ala Gly
                165                 170                 175

Ile Ile Ile Glu Val Ile Gln Gly Glu Gly Gly Val Asn Glu Ala Ser
            180                 185                 190

Glu Asp Phe Leu Ser Lys Leu Gln Glu Ile Cys Lys Glu Lys Asp Val
        195                 200                 205

Leu Leu Ile Ile Asp Glu Val Gln Thr Gly Ile Gly Arg Thr Gly Glu
    210                 215                 220

Phe Tyr Ala Tyr Gln His Phe Asn Leu Lys Pro Asp Val Ile Ala Leu
225                 230                 235                 240

Ala Lys Gly Leu Gly Gly Gly Val Pro Ile Gly Ala Ile Leu Ala Arg
                245                 250                 255

Glu Glu Val Ala Gln Ser Phe Thr Pro Gly Ser His Gly Ser Thr Phe
            260                 265                 270

Gly Gly Asn Pro Leu Ala Cys Arg Ala Gly Thr Val Val Val Asp Glu
        275                 280                 285

Val Glu Lys Leu Leu Pro His Val Arg Glu Val Gly Asn Tyr Phe Lys
    290                 295                 300

Glu Lys Leu Lys Glu Leu Gly Lys Gly Lys Val Lys Gly Arg Gly Leu
305                 310                 315                 320

Met Leu Gly Leu Glu Leu Glu Arg Glu Cys Lys Asp Tyr Val Leu Lys
                325                 330                 335

Ala Leu Glu Arg Asp Phe Ser
            340
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 398 AMINO ACIDS
(B) TYPE: AMINO ACID
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: PROTEIN

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
Met Arg Lys Leu Ala Glu Arg Ala Gln Lys Leu Ser Pro Ser Pro Thr
                5                  10                  15

Leu Ser Val Asp Thr Lys Ala Lys Glu Leu Leu Arg Gln Gly Glu Arg
            20                  25                  30

Val Ile Asn Phe Gly Ala Gly Glu Pro Asp Phe Asp Thr Pro Glu His
        35                  40                  45

Ile Lys Glu Ala Ala Lys Arg Ala Leu Asp Gln Gly Phe Thr Lys Tyr
    50                  55                  60

Thr Pro Val Ala Gly Ile Leu Pro Leu Arg Glu Ala Ile Cys Glu Lys
65                  70                  75                  80

Leu Tyr Arg Asp Asn Gln Leu Glu Tyr Ser Pro Asn Glu Ile Val Val
                85                  90                  95

Ser Cys Gly Ala Lys His Ser Ile Phe Asn Ala Leu Gln Val Leu Leu
            100                 105                 110

Asp Pro Gly Asp Glu Val Ile Ile Pro Val Pro Tyr Trp Thr Ser Tyr
        115                 120                 125

Pro Glu Gln Val Lys Leu Ala Gly Gly Val Pro Val Phe Val Pro Thr
    130                 135                 140

Ser Pro Glu Asn Asp Phe Lys Leu Arg Pro Glu Asp Leu Arg Ala Ala
145                 150                 155                 160

Val Thr Pro Arg Thr Arg Leu Leu Ile Leu Asn Ser Pro Ala Asn Pro
                165                 170                 175

Thr Gly Thr Val Tyr Arg Arg Glu Glu Leu Ile Gly Leu Ala Glu Val
            180                 185                 190

Ala Leu Glu Ala Asp Leu Trp Ile Leu Ser Asp Glu Ile Tyr Glu Lys
        195                 200                 205

Leu Ile Tyr Asp Gly Met Glu His Val Ser Ile Ala Ala Leu Asp Pro
    210                 215                 220

Glu Val Lys Lys Arg Thr Ile Val Val Asn Gly Val Ser Lys Ala Tyr
225                 230                 235                 240

Ala Met Thr Gly Trp Arg Ile Gly Tyr Ala Ala Ala Pro Arg Pro Ile
                245                 250                 255

Ala Gln Ala Met Thr Asn Leu Gln Ser His Ser Thr Ser Asn Pro Thr
            260                 265                 270

Ser Val Ala Gln Ala Ala Ala Leu Ala Ala Leu Lys Gly Pro Gln Glu
        275                 280                 285

Pro Val Glu Asn Met Arg Arg Ala Phe Gln Lys Arg Arg Asp Phe Ile
    290                 295                 300

Trp Gln Tyr Leu Asn Ser Leu Pro Gly Val Arg Cys Pro Lys Pro Leu
305                 310                 315                 320
```

```
Gly Ala Phe Tyr Val Phe Pro Glu Val Glu Arg Ala Phe Gly Pro Pro
                325                 330                 335

Ser Lys Arg Thr Gly Asn Thr Thr Ala Ser Asp Leu Ala Leu Phe Leu
            340                 345                 350

Leu Glu Glu Ile Lys Val Ala Thr Val Ala Gly Ala Ala Phe Gly Asp
        355                 360                 365

Asp Arg Tyr Leu Arg Phe Ser Tyr Ala Leu Arg Leu Glu Asp Ile Glu
    370                 375                 380

Glu Gly Met Gln Arg Phe Lys Glu Leu Ile Glu Ala Ala Leu
385                 390                 395
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 592 AMINO ACIDS
(B) TYPE: AMINO ACID
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: PROTEIN

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Met Cys Gly Ile Val Gly Tyr Val Gly Arg Asp Leu Ala Leu Pro Ile
                  5                  10                  15

Val Leu Gly Ala Leu Glu Arg Leu Glu Tyr Arg Gly Tyr Asp Ser Ala
             20                  25                  30

Gly Val Ala Leu Ile Glu Asp Gly Lys Leu Ile Val Glu Lys Lys Lys
         35                  40                  45

Gly Lys Ile Arg Glu Leu Val Lys Ala Leu Trp Gly Lys Asp Tyr Lys
     50                  55                  60

Ala Lys Thr Gly Ile Gly His Thr Arg Trp Ala Thr His Gly Lys Pro
 65                  70                  75                  80

Thr Asp Glu Asn Ala His Pro His Thr Asp Glu Lys Gly Glu Phe Ala
                 85                  90                  95

Val Val His Asn Gly Ile Ile Glu Asn Tyr Leu Glu Leu Lys Glu Glu
            100                 105                 110

Leu Lys Lys Glu Gly Val Lys Phe Arg Ser Glu Thr Asp Thr Glu Val
        115                 120                 125

Ile Ala His Leu Ile Ala Lys Asn Tyr Arg Gly Asp Leu Leu Glu Ala
    130                 135                 140

Val Leu Lys Thr Val Lys Lys Leu Lys Gly Ala Phe Ala Phe Ala Val
145                 150                 155                 160

Ile Thr Val His Glu Pro Asn Arg Leu Ile Gly Val Lys Gln Gly Ser
                165                 170                 175

Pro Leu Ile Val Gly Leu Gly Glu Gly Glu Asn Phe Leu Ala Ser Asp
            180                 185                 190
```

Ile Pro Ala Ile Leu Pro Tyr Thr Lys Lys Ile Ile Val Leu Asp Asp
195 200 205

Gly Glu Ile Ala Asp Leu Thr Pro Asp Thr Val Asn Ile Tyr Asn Phe
210 215 220

Glu Gly Glu Pro Val Ser Lys Glu Val Met Ile Thr Pro Trp Asp Leu
225 230 235 240

Val Ser Ala Glu Lys Gly Gly Phe Lys His Phe Met Leu Lys Glu Ile
245 250 255

Tyr Glu Gln Pro Lys Ala Ile Asn Asp Thr Leu Lys Gly Phe Leu Ser
260 265 270

Thr Glu Asp Ala Ile Pro Phe Lys Leu Lys Asp Phe Arg Arg Val Leu
275 280 285

Ile Ile Ala Cys Gly Thr Ser Tyr His Ala Gly Phe Val Gly Lys Tyr
290 295 300

Trp Ile Glu Arg Phe Ala Gly Val Pro Thr Glu Val Ile Tyr Ala Ser
305 310 315 320

Glu Phe Arg Tyr Ala Asp Val Pro Val Ser Asp Lys Asp Ile Val Ile
325 330 335

Gly Ile Ser Gln Ser Gly Glu Thr Ala Asp Thr Lys Phe Ala Leu Gln
340 345 350

Ser Ala Lys Glu Lys Gly Ala Phe Thr Val Gly Leu Val Asn Val Val
355 360 365

Gly Ser Ala Ile Asp Arg Glu Ser Asp Phe Ser Leu His Thr His Ala
370 375 380
Gly Pro Glu Ile Gly Val Ala Ala Thr Lys Thr Phe Thr Ala Gln Phe
385 390 395 400

Thr Ala Leu Tyr Ala Leu Ser Val Arg Glu Ser Glu Glu Arg Glu Asn
405 410 415

Leu Ile Arg Leu Leu Glu Lys Val Pro Ser Leu Val Glu Gln Thr Leu
420 425 430

Asn Thr Ala Glu Glu Val Glu Lys Val Ala Glu Lys Tyr Met Lys Lys
435 440 445

Lys Asn Met Leu Tyr Leu Gly Arg Tyr Leu Asn Tyr Pro Ile Ala Leu
450 455 460

Glu Gly Ala Leu Lys Leu Lys Glu Ile Ser Tyr Ile His Ala Glu Gly
465 470 475 480

Tyr Pro Ala Gly Glu Met Lys His Gly Pro Ile Ala Leu Ile Asp Glu
485 490 495

Asn Met Pro Val Val Val Ile Ala Pro Lys Asp Arg Val Tyr Glu Lys
500 505 510

```
Ile Leu Ser Asn Val Glu Glu Val Leu Ala Arg Lys Gly Arg Val Ile
        515                 520                 525

Ser Val Gly Phe Lys Gly Asp Glu Thr Leu Lys Ser Lys Ser Glu Ser
    530                 535                 540

Val Met Glu Ile Pro Lys Ala Glu Glu Pro Ile Thr Pro Phe Leu Thr
545                 550                 555                 560

Val Ile Pro Leu Gln Leu Phe Ala Tyr Phe Ile Ala Ser Lys Leu Gly
                565                 570                 575

Leu Asp Val Asp Gln Pro Arg Asn Leu Ala Lys Thr Val Thr Val Glu
            580                 585                 590
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 354 AMINO ACIDS
(B) TYPE: AMINO ACID
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: PROTEIN

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
Met Ile Pro Gln Arg Ile Lys Glu Leu Glu Ala Tyr Lys Thr Glu Val
                  5                  10                  15

Thr Pro Ala Ser Val Arg Leu Ser Ser Asn Glu Phe Pro Tyr Asp Phe
             20                  25                  30

Pro Glu Glu Ile Lys Gln Arg Ala Leu Glu Glu Leu Lys Lys Val Pro
         35                  40                  45

Leu Asn Lys Tyr Pro Asp Pro Glu Ala Lys Glu Leu Lys Ala Val Leu
     50                  55                  60

Ala Asp Phe Phe Gly Val Lys Glu Glu Asn Leu Val Leu Gly Asn Gly
65                  70                  75                  80

Ser Asp Glu Leu Ile Tyr Tyr Leu Ser Ile Ala Ile Gly Glu Leu Tyr
                 85                  90                  95

Ile Pro Val Tyr Ile Pro Val Pro Thr Phe Pro Met Tyr Glu Ile Ser
            100                 105                 110

Ala Lys Val Leu Gly Arg Pro Leu Val Lys Val Gln Leu Asp Glu Asn
        115                 120                 125

Phe Asp Ile Asp Leu Glu Arg Ser Ile Glu Leu Ile Glu Lys Glu Lys
    130                 135                 140

Pro Val Leu Gly Tyr Phe Ala Tyr Pro Asn Asn Pro Thr Gly Asn Leu
145                 150                 155                 160

Phe Ser Arg Gly Lys Ile Glu Glu Ile Arg Asn Arg Gly Val Phe Cys
                165                 170                 175

Val Ile Asp Glu Ala Tyr Tyr His Tyr Ser Gly Glu Thr Phe Leu Glu
            180                 185                 190
```

```
Asp Ala Leu Lys Arg Glu Asp Thr Val Val Leu Arg Thr Leu Ser Lys
        195                 200                 205

Ile Gly Met Ala Ser Leu Arg Val Gly Ile Leu Ile Gly Lys Gly Glu
    210                 215                 220

Ile Val Ser Glu Ile Asn Lys Val Arg Leu Pro Phe Asn Val Thr Tyr
225                 230                 235                 240

Pro Ser Gln Val Met Ala Lys Val Leu Leu Thr Glu Gly Arg Glu Phe
                245                 250                 255

Leu Met Glu Lys Ile Gln Glu Val Val Thr Glu Arg Glu Arg Met Tyr
            260                 265                 270

Asp Glu Met Lys Lys Ile Glu Gly Val Glu Val Phe Pro Ser Lys Ala
        275                 280                 285

Asn Phe Leu Leu Phe Arg Thr Pro Tyr Pro Ala His Glu Val Tyr Gln
    290                 295                 300

Glu Leu Leu Lys Arg Asp Val Leu Val Arg Asn Val Ser Tyr Met Glu
305                 310                 315                 320

Gly Leu Gln Lys Cys Leu Arg Val Ser Val Gly Lys Pro Glu Glu Asn
                325                 330                 335

Asn Lys Phe Leu Glu Ala Leu Glu Glu Ser Ile Lys Ser Leu Ser Ser
            340                 345                 350

Ser Leu
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 303 AMINO ACIDS
(B) TYPE: AMINO ACID
(D) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE: PROTEIN

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
Met Lys Pro Tyr Ala Lys Tyr Ile Trp Leu Asp Gly Arg Ile Leu Lys
                5                   10                  15

Trp Glu Asp Ala Lys Ile His Val Leu Thr His Ala Leu His Tyr Gly
            20                  25                  30

Thr Ser Ile Phe Glu Gly Ile Arg Gly Tyr Trp Asn Gly Asp Asn Leu
        35                  40                  45

Leu Val Phe Arg Leu Glu Glu His Ile Asp Arg Met Tyr Arg Ser Ala
    50                  55                  60

Lys Ile Leu Gly Ile Asn Ile Pro Tyr Thr Arg Glu Glu Val Arg Gln
65                  70                  75                  80

Ala Val Leu Glu Thr Ile Lys Ala Asn Asn Phe Arg Glu Asp Val Tyr
                85                  90                  95
```

```
Ile Arg Pro Val Ala Phe Val Ala Ser Gln Thr Val Thr Leu Asp Ile
            100                 105                 110

Arg Asn Leu Glu Val Ser Leu Ala Val Ile Val Phe Pro Phe Gly Lys
        115                 120                 125

Tyr Leu Ser Pro Asn Gly Ile Lys Ala Thr Ile Val Ser Trp Arg Arg
    130                 135                 140

Val His Asn Thr Met Leu Pro Val Met Ala Lys Ile Gly Gly Ile Tyr
145                 150                 155                 160

Val Asn Ser Val Leu Ala Leu Val Glu Ala Arg Ser Arg Gly Phe Asp
                165                 170                 175

Glu Ala Leu Leu Met Asp Val Asn Gly Tyr Val Val Glu Gly Ser Gly
            180                 185                 190

Glu Asn Ile Phe Ile Val Arg Gly Gly Arg Leu Phe Thr Pro Pro Val
        195                 200                 205

His Glu Ser Ile Leu Glu Gly Ile Thr Arg Asp Thr Val Ile Lys Leu
    210                 215                 220

Ser Gly Asp Val Gly Leu Arg Val Glu Glu Lys Pro Ile Thr Arg Glu
225                 230                 235                 240

Glu Val Tyr Thr Ala Asp Glu Val Phe Leu Val Gly Thr Ala Ala Glu
                245                 250                 255

Ile Thr Pro Val Val Glu Val Asp Gly Arg Thr Ile Gly Thr Gly Lys
            260                 265                 270

Pro Gly Pro Ile Thr Thr Lys Ile Ala Glu Leu Tyr Ser Asn Val Val
        275                 280                 285

Arg Gly Lys Val Glu Lys Tyr Leu Asn Trp Ile Thr Pro Val Tyr
    290                 295                 300
```